VA UPSTATE NEW YORK HEALTHCARE SYSTEM

STANDARD OPERATING PROCEDURES FOR HUMAN STUDIES RESEARCH

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Standard Operating Procedures For Human Studies Research

Department of Veterans Affairs, Albany, New York

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INTRODUCTION

Standard Operating Procedures For Human Studies Research

Department of Veterans Affairs, Albany, New York

The VA Medical Center Institutional Review Board's (IRB) Standard Operating Procedure (SOP) is a reference for investigators and IRB members. This manual was developed to serve two purposes:

1. to describe the functions and procedures followed by the Institutional Review Board (IRB) of the Research and Development (R&D) Committee at the VA Upstate New York Healthcare System (VAUNYHS), Albany New York that ensure the protection of human subjects as outlined by Federal regulations and Department of Veterans Affairs (DVA) policy, and

2. to outline for investigators the procedures and requirements for submitting human research proposals for review by the IRB, and for the subsequent conduct of that research.

The Institutional Review Board (IRB), previously referred to in the DVA as the Human Studies Subcommittee (HSS), enforces the federal policies and procedures as dictated by the Department of Veterans Affairs (VA Headquarters and the local facility) and also by the Office for Human Research Protection (OHRP) and the Food and Drug Administration (FDA), under the auspices of the US Public Health Service. The DVA is one of 16 departments and agencies, which follow the Federal Policy for the Protection of Human Subjects (also known as The Common Rule, effective August 19, 1991).

INR 2C (4)

This Standard Operating Procedure (SOP) will be reviewed at least annually to incorporate any changes necessary in response to VA and/or federal regulations regarding protection of human subjects. The IRB, the Research and Development Committee, and others, as needed, will participate in the review.

Each investigator will be directed to read *The Belmont Report, The Declaration of Helsinki, The Common Rule* (38 CFR 16), and 45 CFR Part 46 which are on the VISN 2 website and available in the Research Office, and have access to Federal and VA regulations, and the VAUNYHS Manual of IRB Standard Operating Procedures (SOP).

INR 1A (4)

This SOP is part of the systematic and comprehensive "Human Research Protection Program" (HRPP) at the VA Upstate New York Healthcare System (VAUNYHS) with dedicated resources to ensure the rights, safety, and well being of human research subjects participating in research activities.

An HRPP is a comprehensive system to ensure the protection of human subjects participating in research [VHA Handbook 1200.5, 3.f., July 15, 2003]. The HRPP consists of a variety of individuals and committees such as: the Medical Center Director, Associate Chief of Staff (ACOS) for Research and Development (R&D), the Administrative Officer (AO) for R&D, Research Compliance Officer, the R&D Committee, the IRB, other committees addressing human subject protection (e.g., Biosafety, Radiation Safety), investigators, IRB staff, research staff, health

and safety staff (e.g. Biosafety Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

INR 1D (1), (2), (3), (4), (5)

The HRPP program also includes a performance improvement plan and an assessment of resources plan. The Research and Development (R&D) Committee will annually review the budgeting process and the organizational structure for human subjects research (Resource Plan of the HRPP) to ensure adequate resources are available to promptly carry out its functions. The IRB and the Research Administration Office staff will provide information (feedback) on these issues. The annual review will encompass an evaluation of the volume of research, FTE, computer resources, meeting area, filing space, reproduction equipment, databases, supplies, office space, capital equipment, training and education, and any other items as needed. The annual evaluation is submitted to the Research & Development Committee for review and comment, and reviewed by the Medical Center Director in the R&D minutes.

The HRPP program will attain and maintain NCQA accreditation.

A. HUMAN RESEARCH

Chapter 1: Ethical Mandate to Protect Human Subjects

The basic ethical principles guiding research involving human subjects are described in the following documents.

a. **The Nuremberg Code.** The modern history of human subject protections begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related human research experiments. The Nuremberg Military Tribunal developed ten principles as a means of judging their "research" practices, known as *The Nuremberg Code*. The significance of the Code is that it addressed the necessity of requiring the voluntary consent of the human subject and that any individual "who initiates, directs, or engages in the experiment" must bear personal responsibility for ensuring the quality of consent.

b. **The Declaration of Helsinki.** Similar principles to The Nuremberg Code have been articulated and expanded in later codes, such as the World Medical Association *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1964, revised 1975, 1983, 1989, 1996, 2000, with a footnote added in 2002),* which call for prior approval and ongoing monitoring of research by independent ethical review committees.

c. **The Belmont Report.** Revelations in the early 1970s about the 40-year United States Public Health Service Study of Untreated Syphilis in the Negro Male at Tuskegee and other ethically questionable research resulted in 1974 legislation calling for regulations to protect human subjects and for a national commission to examine ethical issues related to human subject research (i.e., the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research). The Commission's final report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, defines the ethical principles and guidelines for the protection of human subjects.

   Perhaps the most important contribution of *The Belmont Report* is its elucidation of three basic ethical principles:

   (1) Respect for persons (applied by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations);

(2) Beneficence (applied by weighing risks and benefits); and

(3) Justice (applied by the equitable selection of subjects).

The Belmont Report also provides important guidance regarding the boundaries and interface between biomedical research and the practice of medicine.

Chapter 2: Regulatory Mandate to Protect Human Subjects

Department of Veterans Affairs (VA) and other Federal regulations require specific protections for human subjects:

a. **Department of Health and Human Services (DHHS) Regulations at 45 CFR 46.** In May of 1974, the Department of Health, Education, and Welfare (later renamed DHHS) codified its basic human subject protection regulations at 45 CFR 46, Subpart A. Revised in 1981 and 1991, the DHHS regulations presently include additional protections for fetuses, pregnant women, and human in vitro fertilization (Subpart B), prisoners (Subpart C), and children (Subpart D). The DHHS regulations are enforced by the Office for Human Research Protections (OHRP).

b. **Department of Veterans Affairs (VA) Regulations at 38 CFR 16 and the Federal Policy (Common Rule) for the Protection of Human Subjects. In addition, 38 CFR 17.33 provides regulations for patient rights. 38 CFR 17.85 discusses treatment of research related injuries to human subjects. 38 CFR 17.45 is Medical Hospital Care for Research Purposes. 38 CFR 17.92 is Outpatient Care for Research Purposes.** In January of 1991, the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified by the VA at 38 CFR 16, the Common Rule is the same as that codified by DHHS as Subpart A of the DHHS regulations at 45 CFR 46, but does not include the additional DHHS Subparts.

c. **Food and Drug Administration (FDA) Regulations at 21 CFR 50 and 56.** When DHHS revised its regulations in 1981, the FDA codified almost identical informed consent regulations at 21 CFR 50 and IRB regulations at 21 CFR 56. Additional FDA regulations that are relevant to the protection of human subjects are:

(1) Investigational New Drug Applications (IND) (21 CFR 312)

(2) Radioactive Drugs (21 CFR 361)

(3) Biological Products (21 CFR 600)

(4) Investigational Device Exemptions (IDE) (21 CFR 812)

INR 1A (1) & (5)

d. **The Assurance and IRB Registration Process.** The VA Upstate New York Healthcare System has its own Federal-Wide Assurance (FWA00002073) and the IRB is also registered (IRB00000950) under this assurance number.

Chapter 3: Types of Human Subject Research and Institutional Review Board (IRB) Considerations

All VA research involving human subjects must be reviewed prospectively by a VA-designated Institutional Review Board (IRB).

a. **Definition of Human Subject Research.** VA regulations at 38 CFR 16.102(d) and the Common Rule define research as a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

VA regulations at 38 CFR 16.102(f) and the Common Rule define human subject as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information." Private information includes information that an individual can reasonably expect will not be made public, and information about behavior that an individual can reasonably expect will not be observed or recorded. Identifiable means that the identity of the individual is or may readily be ascertained by the investigator or associated with the information.

If a FDA-regulated test article is involved, the FDA regulations will also apply. It is important to note that the definitions of "human subject" and "research" in the FDA regulations differ from the VA regulations and the Common Rule. In 21 CFR 56.102(c), the FDA regulations define research as "… any experiment that involves a test article and one or more human subjects…." The FDA regulation further states that "…The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part." 21 CFR 56.102(e) defines human subject as "an individual who is or becomes a subject in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."

1. **Examples of Human Subject Research.** The following examples illustrate common types of human subject research. These are examples

only, and are not exhaustive of all human subject research conducted at the VA. They may be done at one VAMC or may be conducted as multi-center projects (i.e., VA Cooperative Studies Program).

(a) **Clinical Research.** Clinical research involves research: (a) to increase scientific understanding about normal or abnormal physiology, disease states, or development and (b) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of clinical research. As defined in the FDA regulations, clinical investigation means any experiment that involves a test article and one or more human subjects. (21 CFR 56.102) The terms research, clinical research, clinical study, and clinical investigation are generally considered to be synonymous.

(b) **Behavioral and Social Sciences Research.** The goal of behavioral and social research is similar to that of clinical research — to establish a body of knowledge and to evaluate interventions — but the content and procedures often differ. Social and behavioral research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention.

(c) **Epidemiological Research.** Epidemiological research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, efficiency, interventions, or delivery of services to affected populations. Some epidemiological research is conducted through surveillance, monitoring, and reporting programs — such as those employed by the Centers for Disease Control and Prevention (CDC) — whereas other epidemiological research may employ retrospective review of medical, public health, and/or other records. Because epidemiological research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. If an investigator believes this is the case, the PI must submit the research to the IRB Chair or designee to determine if it qualifies for an exemption or might be considered for expedited review.

IRB 4D (2)

IRB 4C (2)

(d) **Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a VA-sponsored tissue bank or a VA-approved bank or repository for use in future research, the IRB will review a protocol detailing the

repository's policies and procedures for obtaining, storing, destruction of specimens, and sharing of resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with or without IRB review of individual research protocols.

(e) **Quality Assurance/Quality Improvement Activities.** Quality assurance activities attempt to measure the effectiveness of programs or services. Such activities may constitute human subject research, and if they are designed or intended to contribute to generalizable knowledge, they require IRB review. Quality assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, will probably not require IRB review or will qualify for an exemption. In all cases, the IRB Chair or designee, not the individual investigator, will determine when IRB review of such activities is required.

IRB 4C (1)

IRB 4D (1)

(f) **Surveillance Activities.** The same distinction may apply to routine surveillance activities. For example, what began as a disease outbreak investigation by a public health agency may evolve into a research project. The researchers are obligated to subject the research activity to the appropriate level of human subjects review as soon as the intent of the data collection or analysis changes. Often, the research activity for review consists of secondary analysis of the outbreak data collected originally for the purpose of protecting the public health.

(g) **Pilot Studies.** Pilot studies involving human subjects are considered human subject research and require IRB review.

(h) **Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (f) gene frequency studies. Unlike the risks presented by many biomedical research protocols, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and

employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. Because this is a developing field, there are some issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists. OHRP representatives have advised that "third parties," about whom identifiable and private information is collected in the course of research, are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB's can consider whether informed consent from third parties can be waived in accordance with 38 CFR 16.116 and if so, document that in the IRB minutes.

ICS 2A (1)

(i) **Tissue Bank**. Human biological specimens, as well as the linked clinical data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, are maintained at VA approved tissue banks (VHA Directive 2000-043, November 6, 2000).

IRB 4C (1) ,(2)
IRB 4D
IRB 4A (2)
IRB 4B (1)
IRB 4A (1)

Selected types of research are exempt from Institutional Review Board review because they are considered to pose no risk to subjects. However these studies are reviewed and approved by the VAUNYHS Institutional Review Board.

Research activities involving "no more than minimal risk" and in which the involvement of human subjects will be in one or more of the identified categories may be reviewed using an expedited review procedure by the IRB. Based on qualifications, training and experience, the IRB Chair or designee review proposals for compliance with VA and Federal regulations for expedited review. If the proposal meets the criteria for expedited review, the IRB Chair or his designee conducts the review and reports the findings to the next full-convened IRB meeting. Designees are voting members of the IRB with at least one-year experience on the IRB.

All research that is not eligible for exempt review or minimal risk (expedited) review must be reviewed by the full Institutional Review Board.

B. INSTITUTIONAL REVIEW BOARD ADMINISTRATION

Chapter 4: Shared Responsibilities for Protecting Human Subjects

The ethical conduct of research is a shared responsibility. It requires cooperation, collaboration, and trust between the institution, investigators and their research staff, the subjects who enroll in research, and the Institutional Review Board (IRB) members and staff. A clear delineation of the responsibilities of each of these parties in the IRB SOP helps assure protections for the subjects who volunteer for research.

a. **The Medical Center Management (38 CFR 16.103).** The Medical Center Director of the facility is the Assurance Signatory Official (responsible institutional official) and is ultimately responsible for overseeing the protection of human subjects within the facility. The Signatory Official must also ensure that open channels of communication are maintained between the IRB, research investigators and staff, and facility management, and that the IRB is provided with sufficient meeting space and staff to support its substantial review and confidential record keeping responsibilities.

INR 1A (2)

The VA Upstate New York Healthcare System at Albany has a systematic and comprehensive program, "Human Research Protection Program" (HRPP) with dedicated resources to ensure the rights, safety and well being of human research subjects in relation to their participation in research activities. As stated previously, the HRPP embraces the basic ethical principles identified in *The Belmont Report*. The Medical Center Director is responsible for the HRPP and is assisted by members of the Institutional Review Board, and the Associate Chief of Staff (ACOS) for Research and Development, Administrative Officer (AO) to the ACOS, Research Office Staff, and research compliance officer. The Conflict of Interest Administrator will review any possible issues of conflict of interest of study personnel prior to approval of research by the IRB or R&D Committee.

INR 3A (3)

While the Medical Center Director is responsible for the HRPP, the Institutional Review Board and the Research and Development Committee ensure that the HRPP is operational. Specifically, the IRB is responsible for:

INR 1B (1), (2), (3), (4)

- implementation of the institution's HRPP policy;
- review and evaluation of the reports and results of compliance assessment and quality improvement activities;

INR 5A

- implementation of needed improvement and follow-up on actions, as appropriate;
- monitoring changes in VA and other Federal regulations and policies that relate to human research protections.

b. **The Institutional Review Board (IRB).** The Institutional Review Board is a formally established subcommittee of the Research and Development (R&D) Committee. (M-3, Part 1, Chapter 2.02 and 3.01). The IRB is an appropriately constituted group that the VA has designated to review and monitor research involving human subjects to protect the rights and welfare of the subjects. The IRB also provides oversight and monitoring of such protections. In accordance with the Common Rule, VA and FDA regulations, the IRB has responsibility for approving, requiring modification (to secure approval), or disapproving research. Members of the IRB receive various regulatory and historical background reference information and complete training on Human Research Protections as outlined in the IRB member training policy. They also have access to electronic versions of recommended reading materials on the VAUNYHS research website and in the Research Office.

The Medical Center recognizes the IRB as the reviewing body for ethical issues involving research protocols, and the FDA recognizes the IRB as its reviewing body at the local level, established to protect the rights and welfare of human research subjects recruited to participate in research activities conducted under the auspices of the VAUNYHS at Albany. All research involving human subjects conducted completely or partially in this DVA facility, including research funded from extra-DVA sources and research conducted without direct funding, must be reviewed and approved by the VAUNYHS Institutional Review Board (VHA Handbook 1200.5, 4.b., July 15, 2003).

INR 1A (5)

INR 2C (1)

The ACOS for Research and Development assesses the qualifications and experience of the IRB Chair prior to making a recommendation to the Medical Center Director. The Medical Center Director appoints the members of the IRB based on recommendations by IRB members and R&D members. It is the responsibility of the Institutional Review Board to ensure that due care is taken to protect human research subjects. Additionally, the IRB will protect the confidentiality of subjects, protocols, and the data generated during the research. Approval of this IRB is a prerequisite to conduct human studies research within this Medical Center.

c. **The Research and Development Committee (R&D).** The R&D Committee is the scientific review body for all research activities and is assisted by the Institutional Review Board. The R&D Committee reports to the Medical Center Director, who is the institutional officer accountable

for all research activities conducted at the Stratton VAMC in Albany. The R&D Committee is responsible for assuring the scientific quality and appropriateness of all research involving human subjects, the protection of human subjects, the welfare of animal research subjects, and laboratory safety. The R&D Committee assesses the impact of potential research proposals on the VAUNYHS at Albany, and its Care Lines, and advises the ACOS/R&D and the Medical Center Director on professional and administrative aspects of proposals. All R&D Committee activities within the facility, whether funded or unfunded, are within its purview. The R&D Committee re-evaluates, at least annually, the scientific quality of all research studies involving human subjects to ensure the protection of human subjects. Membership on the R&D Committee is supplemented, as needed, by consultants or permanent members who possess additional expertise that may be required to perform the scientific review. The R&D Committee cannot alter an adverse report or recommendation, e.g., disapproval for ethical or legal reasons, made by the Institutional Review Board. The Medical Center Director receives an approved signed copy of the minutes of the Research and Development Committee.

IRB 4D (2)

IRB 4C (2)

IRB 5B (2)

All studies conducted on healthy individuals or patients at the Medical Center, whether by full-time or part-time employees or by individuals without compensation appointments (WOC) of the Medical Center, must be approved by the Medical Center Institutional Review Board and the Research and Development Committee. VA patients may also be recruited for non-VA studies. Research reviewed by the IRB Chair or designee or the full committee is reported in the IRB minutes to the R&D Committee.

Members of the Research and Development Committee receive various regulatory and historical background information and complete the same training as IRB members. They also have access to electronic versions of recommended reading materials on the VAUNYHS research website and in the Research Office.

The Research and Development Committee reviews the total research effort of investigators, which includes the number of studies in progress by a PI and any overlap of proposals.

d. **The Principal Investigator (VHA Handbook 1200.5, 10., July 15, 2003).** As the individual responsible for the implementation of research, the principal investigator assumes direct responsibility for ensuring the protection of every research subject. This responsibility starts with protocol design, which must minimize risks to subjects while maximizing research benefits. In addition, the principal investigator must ensure that all members of the research team always comply with the findings, determinations, relevant policies and regulations listed above, and

CRB 2A (2)

INR 6C (5)

requirements of the IRB. The principal investigator must also ensure the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team are authorized to actually obtain and document consent.

Principal investigators are responsible for ensuring that (1) all human subject research that they conduct in the VAMC, as employees or agents of the VA, has received initial review and approval by an IRB; (2) once the project is approved, continuing review and approval of the research has been accomplished appropriate to the degree of risk and not less than one time per year; and (3) the research is conducted at all times in compliance with all applicable regulatory requirements and the determinations of the IRB. The IRB will not retroactively approve research conducted with human subjects.

No changes in approved research may be initiated without prior IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects; and no research may be continued beyond the IRB-designated approval period (38 CFR 16.103).

CRB 2A (1)

Investigators must notify the IRB promptly of (1) any serious adverse events or unanticipated problems involving risks to subjects or others, and (2) any serious or continuing non-compliance with applicable regulatory requirements or determinations of the IRB (21 CFR 56.108(b) and 38 CFR 16.103).

Federal regulations, organizational policies/procedures, and IRB(s) exist to enhance, but cannot replace the investigator's primary role as the protector of the rights and welfare of research subjects.

In addition, investigators are responsible for:

- Ultimately responsible for any and all activities related to the conduct of their research, and for any and all activities performed by any persona ssisting in the conduct of the research.

- being knowledgeable about, and follow all VA and federal regulations, and institutional policies and procedures for the protection of human subjects.

IRB 3A (1)

- submitting all research proposals to the IRB for review and approval.

- ensuring the ethical conduct of their research and the conduct of their research staff. Principal investigators who supervise others in the conduct of research are responsible for ensuring that they

comply with rules and regulations for the use of human subjects in research.

- ensuring that research involving human subjects is reviewed by the Institutional Review Board and the Research and Development Committee before research is initiated.

IRB 3A (2), (8)

- seeking and receiving approval for any proposed changes/amendments to the research protocol prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to subjects, which then need to be reported promptly.

IRB 3A (3)

- submitting proposed changes in the informed consent form or HIPAA authorizations for review and approval.

IRB 3A (5), (6)
CRB 2A (1)

- reporting to the Institutional Review Board any unanticipated problems, serious and unexpected adverse events, and any changes in risks/benefits to subjects.

IRB 3A (4)

- reporting deviations from the procedures stated in the approved research protocol or informed consent.

- submitting all required information at the time of continuing review.

IRB 3A (7)

- ensuring that research staff have received the appropriate educational training to safely assist in the conduct of the research study.

- Successfully completing all the required and appropriate educational training, and other IRB requirements to safely conduct human subject research.

- maintaining case histories for all research subjects.

- retaining copies of all study documents and correspondence with the Institutional Review Board.

- ensuring that the research is conducted according to the research protocol approved by Institutional Review Board.

IRB 3A (10)

- including a qualified clinician to be responsible for all study-related healthcare decisions in clinical interventional studies.

IRB 3A (9)

- promptly reporting to the IRB changes in the status of the research study such as study completion or termination, or a change in Principal Investigator.
- identifying and complying with financial disclosure statements.
- assuring fiscal management, if applicable.
- complying with the terms and conditions of a sponsor's award, if applicable.
- ensuring that a qualified individual is responsible for the conduct of the study in the absence of the PI (i.e. vacation).

Qualifications of Investigators. The Institutional Review Board will consider research proposals submitted by qualified investigators who are employees of the VAUNYHS at Albany, or who hold a WOC appointment. The investigator's CV is taken into account and related to the degree of protocol complexity and risk to human subjects. The IRB may require that experienced VA researchers serve as mentors for less experienced research investigators. Proposals that require skills beyond those held by the PI either will be modified to meet the investigator's skills, will have qualified personnel added, or will be disapproved. In general, all physicians and employees with advanced degrees will be considered to be qualified investigators by the IRB if they meet all educational/training requirements, have concurrence from their Care Line Manager, and submit curriculum vitae. The investigator must have the appropriate educational training and be credentialed to conduct research involving human subjects by a program that meets all VA requirements (VHA Handbook 1200.5, 10.a., July 15, 2003).

IRB 4C (2)

IRB 4D (2)

An investigator from outside the VAUNYHS must have a VA collaborating investigator on the project, meet the above-described qualifications, and must receive approval from the collaborating investigator's VA Care Line Manager. Residents and other health professionals in training programs must have a responsible VA investigator as a Co-Principal Investigator on a research study.

The investigators have a strict obligation to comply with all IRB determinations and procedures, adhere rigorously to all protocol requirements, inform staff of all adverse subject reactions or unanticipated problems, ensure the adequacy of the informed consent process, and take measures necessary to ensure adequate protection for subjects by other members of the research team.

e. **Other Members of the Research Team.** Each member of the research team is responsible for human subject protection. Co-investigators, sub-

investigators, study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures, adhere rigorously to all protocol requirements, inform investigators of all adverse subject reactions or unanticipated problems, ensure the adequacy of the informed consent process, and take measures necessary to ensure adequate protection for subjects.

Every member of the research team is responsible for notifying the IRB promptly of any serious or continuing non-compliance with applicable regulatory requirements, or determinations of the designated IRB, of which they become aware, whether or not they themselves are involved in the research.

Chapter 5: IRB Roles and Authorities

Department of Veterans Affairs (DVA) Institutional Review Board derives authority from both regulatory and institutional sources.

a. **Human Subject Protections under VA Regulations (See Federal-Wide Assurance on VA public drive).** VA regulations at 38 CFR 16 and 17 require protections for human subjects in accordance with the Federal Policy (Common Rule) for the Protection of Human Subjects. The regulations require that each VA Medical Center (VAMC) conducting human subject research file a written Assurance of protection for human subjects with VA and the Office for Human Research Protections (OHRP), designating an Institutional Review Board as the IRB of record. The Office for Human Research Protections also requires completion of online educational modules located on the OHRP web site as part of the terms and conditions of Assurance for Federal Wide Assurance (FWA) signatory officials. The VA Network Director and Medical Center Director complete module one of the OHRP online training modules.

INR 1A (1)

INR 6A (1), (2)

INR 1A (3), (5)

b. **Institutional Authority of the IRB (M-3, Part 1, Chapter 2.02 and 3.01).** The VAMC Director is responsible for all research activities conducted under the auspices of the medical center. The Research and Development (R&D) Committee, which reports to the VAMC Director, oversees the designated IRB to review the facility's human subject research program.

The Institutional Official (IO) is the Medical Center Director [VHA Handbook 1200.5, 3.i., July 15, 2003]. The IO is the VA official responsible for ensuring that the HRPP at the facility has the resources and support necessary to comply with all federal regulations and guidelines that govern human subjects research. The IO is legally authorized to represent the institution, is the signatory official for all Assurances, and assumes the obligations of the institution's Assurance. The IO is the point of contact for correspondence addressing human subjects research with OHRP, FDA, and VA Headquarters.

INR 1A (2)

INR 2A

VA policy does not permit use of central commercial IRBs or other non-VA Federal IRB(s).

The IRB that is operated by the VAUNYHS at Albany functions as a subcommittee of the R&D Committee. The R&D Committee is empowered to give final approval for initiation of a study approved by the IRB. The Medical Center Director and R&D Committee cannot alter an adverse report or recommendation by the IRB (M-3, Part 1, Chapter 3.01(e)).

If, in the course of its review, the R&D Committee requires changes to the protocol that may affect the protection of the human subjects, the R&D Committee must refer those changes for the protection of human subjects to the IRB for its approval before the final approval of the R&D Committee.

c. **Purpose of the Institutional Review Board.** The Institutional Review Board's primary responsibility is to ensure that the rights and welfare of subjects are protected in the VAMC human subject research program (38 CFR 16.109). In doing so, the IRB must ensure that the human subject research is conducted ethically, and in compliance with VA and other Federal regulations, the requirements of applicable state law, the VAMC's FWA (or other Assurance), and the VAMC's institutional policies and procedures. Its secondary responsibility is to ensure that all policies and procedures are properly followed by all those involved in human studies research.

INR 1A (4)

INR 6C (1)

d. **Scope of the IRB's Authority (38 CFR 16 & 17; 21 CFR 50 & 56; and 45 CFR 46).** The IRB designated by the VAMC Director and named in the FWA has the authority to approve, require modifications in, or disapprove human subject research (38 CFR 16.109(a)) conducted at the VAUNYHS at Albany. The research may be conducted by VAMC salaried employees or agents, or otherwise under the auspices of the VA (e.g., research using non-public patient data from VA records, using VA resources, published or presented with VA cited as supporting or conducting the research, or recruiting VA patients at VA facilities).

The IRB has the authority to take any action necessary to protect the rights and welfare of human subjects in the VA facility's research program and may suspend or terminate the enrollment and/or the ongoing involvement of human subjects in the research as it determines necessary for the protection of those subjects (38 CFR 16.113).

INR 1A (3)

The IRB has the authority to observe and/or monitor human subject research to whatever extent it considers necessary to protect human subjects, including the review of the informed consent process and procedures used to enroll subjects.

e. **Disagreements Among Designated IRB(s) in Multi-Center Research.** VA Cooperative Studies Program (CSP) Guidelines (January 2001) state that although it is the preference of the CSP that a single standard informed consent form with HIPAA provisions or separate HIPAA authorization be used at all participating medical centers, the ultimate responsibility for the welfare of the subject resides at the individual medical center. If an IRB from a participating medical center makes suggestions for changes, they will be seriously considered. Similarly, local variations can be incorporated into a standard document for use in all or

most medical centers. When necessary and appropriate, variations across centers will be permitted with the approval of the Director, Cooperative Studies Program Coordinating Center (CSPCC). Major changes must have the approval of the CSPCC Human Rights Committee.

f. **Report of IRB Findings and Appeal of IRB Determinations (38 CFR 16.109(d)).** The IRB must provide the investigator with a written statement of its reasons for disapproving or requiring modifications in proposed research, and must give the investigator an opportunity to respond in person or in writing. The IRB evaluates the investigator's response in reaching its final determination.

INR 5B (1)

Notification of IRB contingent approval will include a list of all IRB stipulations that must be met before final IRB approval can be given. Once the IRB has determined that all contingencies have been met, notification of final approval will be made by the IRB Chair or designee.

g. **Other Relationships within the VAMC.**

(1) The IRB may require that proposed research be reviewed and approved by the Albany VAMC's Radiation Safety Committee, the Biohazard Committee, Medication Use Committee, and/or any other relevant committee of the VAUNYHS at Albany.

(2) All persons conducting research within the VAUNYHS, and all persons acting as employees or agents of the VAUNYHS regardless of location, must comply with all requirements of the IRB in the conduct of human research. Such persons must provide the IRB with copies of any reports or correspondence to or from any regulatory or compliance enforcement Federal agency, such as ORO, OHRP, or the Food and Drug Administration (FDA), that exercises oversight over the protection of human subjects in research in which they are involved.

h. **Responsibilities to Regulatory Agencies.** The IRB complies with the requirements of all relevant regulatory and compliance enforcement agencies or offices, including ORO, OHRP, and FDA. Copies of any relevant reports or correspondence to or from such agencies concerning the VAMC's research must be provided by the IRB to the VAMC's Director, who shall determine whether any additional notifications are necessary.

(1) **Allegations of Non-compliance.** Within the VA Medical Center structure, allegations of serious non-compliance must be reported to the IRB Chair, the ACOS for R&D, the Facility Research Compliance Officer, and to the Research & Development Committee.

IRB 3C (4)

(2) **Scientific Research Misconduct.** The VAUNYHS at Albany bears primary responsibility for the prevention and detection of research misconduct within its own facility and for conducting inquiries and investigations when required. The VA has procedures for handling allegations of scientific misconduct.

i. **Responsibility for Human Subject Protection Education Program.** VA policy requires education about human subject protections for research investigators. The institutional policy is created by the IRB Chair or designee, HRPP Coordinator, and the Research Compliance Officer, in collaboration with the ACOS-Research and Medical Center Director. Training records are maintained by the HRPP Coordinator.

INR 6A (1), (2)

TITLE	**Control & Distribution of IRB Standard Operating Procedures**	
Document number	**IRB-000**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/12/2004**

INR 2C

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are used to guide personnel through various procedural steps and standardize practices to ensure subject protection and promote responsible research.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

IRB Standard Operating Procedure Master Log
SOP Scheduled Review Notice form

4 REFERENCE DOCUMENTS

N/A

5 PROCEDURE

5.1 The Research Office is responsible for the preparation and revision of IRB SOPs. The following format must be used when writing IRB SOPs.

5.2 SOP Format

5.2.1 Each first page of an individual SOP procedure will contain a header with the following information:

5.2.1.1 **TITLE:** Title of SOP.

5.2.1.2 **DOCUMENT NUMBER:** Unique number assigned to SOP. This is a sequential alphanumeric designation. Example: IRB-001.

5.2.1.2.1 **IRB** refers to the procedures related to operation and support of the IRB.

5.2.1.2.2 001 designates the sequence number of the SOP. Sequence numbers may range from 000 to 999.

5.2.1.2.3 **SUPERSEDES DOCUMENT DATED:** Effective date of previous version.

5.2.1.2.4 **EFFECTIVE DATE:** Date SOP goes into effect.

5.2.2 SOP Content

5.2.2.1 Each individual SOP will be written with the following section headings:

5.2.2.1.1 **POLICY:** An associated institutional, legal, or safety policy that affects activities described in the SOP.

5.2.2.1.2 **DEFINITIONS:** Reference Appendix A

5.2.2.1.3 **FORMS:** Any equipment or materials needed to perform the activities described in the SOPs.

5.2.2.1.4 **REFERENCE DOCUMENTS:** Any written material referred to in the SOP such as operating manuals, publications, related SOPs, etc.

5.2.2.1.5 **PROCEDURE:** Step-by-step description of all activities to be performed in following SOP directions. A short narrative may be included in this section to further explain, provide background, or clarify procedures.

5.3 Creation of new SOPs

5.3.1 The Research Office assigns a number and title to the new SOP.

5.3.2 The Research Office drafts the SOP and distributes the draft to IRB members to review and approve a final SOP.

5.3.4 The Research Office files the original SOP in the master file and scans the document onto the Public (P) drive.

5.4 SOP Revision

5.4.1 Revisions to an SOP are warranted whenever procedures are changed. These revisions must occur in order to minimize deviations to the stated procedure.

5.4.2 The HRPP Coordinator revises the SOP, and distributes the revision to the IRB to review and approve a final SOP revision.

5.5 SOP Periodic Review

5.5.1 The entire SOP is reviewed at least annually.

5.5.2 The Research Office maintains a review schedule.

5.5.3 The IRB Chair or designee, ACOS R&D, and Compliance designee respond by indicating status of SOP at least 30 days prior to SOP review notice date (e.g. obsolete, revise, no changes), sign and return the Review Notice and the SOP. If the SOP needs to be revised, proceed with section 5.4.

5.6. Distribution and Control of IRB SOPs

5.6.1 The Research Office is responsible for distribution and control of all IRB SOPs.

5.6.2 The Research Office maintains a master file for the SOP in a designated secure place with access limited to Research Office personnel. The master file contains:

5.6.2.1 Original of all current, previous, and obsolete SOP versions.

TITLE	**Initial Review of Research**	
Document number	**IRB-001**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/14/2004**

INR 5A

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH (International Conference on Harmonization) guidelines in the conduct of clinical research studies. Written procedures are required for documenting expedited and full committee review of new protocols, and for reporting the IRB's actions to the Principal Investigator.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

New Protocol Submission Form
Primary Reviewer Form
Report of Subcommittee on Human Studies (VA Form 10-1223)
New Protocol Submission Checklist
Notification of Disapproval letter
HIPAA Authorization
Waiver of HIPAA Authorization
Pharmacy Memorandum D&T 119-9
Investigational Drug Information Record (VA Form 10-9012)
Statement of Investigator (FDA 1572)

4 REFERENCE DOCUMENTS

45 CFR 46

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 Principal Investigators will request review of research by submitting a New Protocol Submission Form, with copies of all supporting documents.

5.2 The IRB Staff checks the investigator education training list to assure the Principal Investigator(s), co-investigators, and sub-investigators are certified and credentialed to submit new research.

5.2.1 If they are not certified and credentialed, the IRB staff will inform the PI of the requirements. Final approval of the research will be contingent upon completion of the educational training requirements for all research staff listed on the New Protocol Submission Form.

5.3 The IRB staff checks the original submission for completeness and accuracy and enters the submission into the database. For example:

5.3.1 Verify that the New Protocol Submission Form has the signatures of the PI(s), all co-investigators, sub-investigators, and Care Line Leader(s).

5.3.2 Verify that if Investigational New Drug(s) (IND) or Investigational Device Exemptions (IDE) will be used, an IND# or IDE# is listed on the New Protocol Submission Form. If an IND# or IDE# is not listed, the IRB staff will not accept the submission from the Principal Investigator(s) or designated contact person until the information is complete.

5.3.3 Verify that an appropriate number of copies of attachments are included according to the New Protocol Submission Checklist.

5.4 If any items are missing, the IRB staff will notify the Principal Investigator(s) or the designated contact person.

5.5 Research that represents no more than minimal risk and falls into one or more categories listed in "Categories of Research That May be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure" may be reviewed by expedited review or by the full IRB. All other research must be reviewed by the full IRB.

5.5.1 The HRPP Coordinator consults with the IRB Chair or designee to discuss whether the research will be processed by full committee review or by expedited review, and documents the decision.

5.6 Expedited Review Process:

5.6.1 A member of the IRB staff pre-reviews the research. The IRB Chair or designee conducts the review.

5.6.2 The IRB Chair or designee conducting expedited review has the final authority in deciding whether the research qualifies for expedited review and may recommend full committee review.

5.6.3 In order to approve research covered by this policy the reviewer shall determine that the research:

5.6.3.1 Represents no more than minimal risk.

5.6.3.2 Falls into one or more "Categories of Research That May be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure".

5.6.3.3 Satisfies the criteria for approval of research (38 CFR 16.111).

5.6.4 If the reviewer requests changes or additional information, the IRB staff contacts the Principal Investigator(s)or the designated contact person and requests the information. Upon receipt of the requested information, the changes or additional information are forwarded to the reviewer.

5.6.5 If the reviewer still cannot approve the research as submitted, the Principal Investigator(s) or designated contact person is notified. The Principal Investigator(s) may modify the research for resubmission to the IRB or resubmit the research for review at a full IRB meeting.

5.6.6 If the reviewer recommends full committee review, the Principal Investigator(s) or designated contact person is notified that the research must be reviewed by the full committee and is asked to provide additional copies of the research submission.

5.6.7 The reviewer may not disapprove new research under Expedited Review.

5.6.8 If the reviewer finds the research acceptable:

5.6.8.1 The IRB Chair or designee who reviewed the research approves the research.

5.6.8.2 The IRB Chair or designee signs and dates the IRB Approval – Initial Review letter, indicating the risk level and the interval of approval.

5.6.8.3 The IRB Approval – Initial Review letter, and approved stamped consent and HIPAA authorization, if applicable, is sent to the Principal Investigator(s).

5.6.8.4 The IRB is notified of the approval in the agenda of the next scheduled IRB meeting.

5.6.8.5 New research approved by Expedited Review receives an interval of approval of no more than 365 days.

5.7 Full Committee Review:

5.7.1 Research that requires full committee review is placed on the agenda of the monthly IRB meeting and is distributed approximately two weeks in advance of the meeting. The agenda identifies all IRB members who are also participating in the research to alert the committee of a conflict of interest.

5.7.2 The IRB staff, with the concurrence of the IRB Chair or designee, assigns two primary reviewers, who are not participating in the research, based on their area of expertise. The IRB Chair or designee is assigned as a 3rd reviewer for all studies.

5.7.3 Primary reviewers are given a copy of the New Protocol Submission Form and the entire research submission, including the protocol, abstract, consent document(s), investigator brochure(s), advertisements, participant materials, Financial Conflict of Interest disclosure forms, HIPAA authorization and/or waiver request, and applicable research grants or budget copies approximately two weeks in advance of the meeting**.**

5.7.3.1 Primary reviewers are provided with a Primary Reviewer Form to record their comments.

5.7.3.2 Committee members who are not primary reviewers are given a copy of the New Protocol Submission Form, the protocol, consent documents, advertising, HIPAA authorization and/or waiver request, and participant materials approximately two weeks in advance of the meeting.

5.7.4 The review of research takes place at the monthly meeting of the IRB.

5.7.5 In order to approve a new research protocol, the IRB shall determine that criteria for approval of research are satisfied (38 CFR 16.111).

5.7.6 The IRB staff takes minutes at the meeting pertaining to discussion of the research and any controverted issues and their resolution.

5.7.7 Minutes are prepared within one week after the meeting and include:

5.7.7.1 Attendance of IRB members at the meeting.

5.7.7.2 The votes for, against, abstaining, recused, and excused, as well as the recommended period of approval. IRB members with a conflicting interest must recuse themselves from voting.

5.7.7.3 Modifications or any other changes to the research required by the IRB.

5.7.7.4 The basis for requiring changes in or disapproving research.

5.7.7.5 A written summary of any discussion of controverted issues and their resolution.

5.7.7.6 Documentation of required IRB findings such as:

5.7.7.6.1 Alteration or waiver of requirements for informed consent

5.7.7.6.2 Waiver of requirement to obtain signed consent

5.7.7.6.3 Research involving vulnerable participants

5.7.8 If the research is approved as submitted:

5.7.8.1 The IRB Chair or designee signs and dates the IRB Approval – Initial Review letter.

5.7.8.1.1. The Date of Approval is the date of the meeting at which the research was approved.

5.7.9 If the research is granted approval with modifications:

5.7.9.1 The modifications must be documented in sufficient detail to allow the IRB staff to verify the changes required by the IRB.

5.7.9.2 A Notification of Approval with Contingencies letter, listing all required modifications and conditions for approval, is sent to the Principal Investigator(s).

5.7.9.3 The Principal Investigator(s) responds to the Research Office with a copy of all modified documents within 3 months.

5.7.9.4 The IRB staff reviews the modified documents for confirmation of all modifications required by the IRB.

5.7.9.5 If the submitted documents have not been modified as required, the Principal Investigator(s) is contacted by IRB staff and asked to submit the complete revision as requested.

5.7.9.6 Once the IRB staff determines that the documents contain all required modifications, the IRB Chair or designee signs the IRB Approval – Initial Review letter.

5.7.9.6.1 The Date of Approval is the date of the meeting at which the research was approved with modifications.

5.7.9.7 If the Principal Investigator(s) does not return the required modified documents within approximately three months, as indicated on the Contingent Approval letter, the IRB Chair or designee notifies the Principal Investigator(s) in writing that the protocol remains unapproved and further consideration of this research will require submission of a new protocol.

5.7.10 If the research is disapproved, the IRB Chair or designee notifies the Principal Investigator(s) in the Notification of Disapproval letter of the reasons for disapproval and offers the Principal Investigator(s) an opportunity to resubmit the research to the IRB within three months.

5.7.10.1 If the Principal Investigator(s) resubmits the research to the IRB, the disapproval letter will be distributed with the agenda and included in the primary reviewer materials for the next scheduled IRB meeting.

5.8 The IRB may require proposed research to be reviewed and approved by the VAMC Radiation Safety Committee, Subcommittee on Research Safety & Biosafety (SRS&B), Institutional Animal Care and Use Subcommittee (IACUC), other committees of the VAMC, relevant committees of collaborating institutions, or by ad hoc reviewers.

5.9 Informed consent forms and HIPAA authorizations associated with approved research are stamped with a Date of Approval and a Date of Expiration. A copy of the stamped consent(s), HIPAA authorizations, and approval letter will be provided to the investigator.

5.9.1 The Date of Approval is defined as the date of the meeting at which the research was approved.

5.9.2 The Date of Expiration is defined as the Date of Approval plus the recommended interval of review.

5.10 The research protocol and copies of documents received and sent are filed in the Research Office.

5.11 The IRB staff files the Primary Reviewer Form with the research submission.

TITLE	**Continuing Review of Research**	
Document number	**IRB-002**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/14/2004**

IRB 3A

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH Guidelines in the conduct of clinical research studies. Written procedures are required for documenting expedited and full committee continuing review of research, and to report the IRB's actions to the Principal Investigator(s).

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Non-Exempt Protocol Progress Report Form
Final Expedited Review Continuation Approval letter
Notification of Approval with Contingencies
Final Continuation Approval letter
Notification of Expiration
Notification of Disapproval letter
Exempt Protocol Progress Report
Protocol Education Report
Primary Reviewer Form

4 REFERENCE DOCUMENTS

45 CFR 46
21 CFR 50, 56
38 CFR 16
VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research
ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 Upon initial or continuing approval of research, the IRB grants an interval of approval appropriate to the degree of risk, but no longer than 365 days. The expiration date of the research (last day of interval of approval) is the

date of the most recent initial or continuing approval plus the interval of approval. The date of the closest IRB meeting before the expiration date is the IRB meeting at which continuing review is scheduled to occur.

5.2 Approximately two months before the date of the IRB meeting at which continuing review is scheduled to occur, the IRB staff sends a Protocol Progress Report Form and the Protocol Education Report to the Principal Investigator.

5.2.1 The Principal Investigator is expected to complete the progress report form and provide all applicable attachments requested on the form.

5.2.1.1 The signature of the Principal Investigator(s) on the progress report ensures that all changes in previously approved research will be reported to the IRB. Proposed changes will not be implemented without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.

5.3 Upon receipt of the progress report from the Principal Investigator(s), the Research Office stamps it with the date of receipt and enters the request into the database.

5.4 If the IRB does not receive an accurate and complete progress report by the submission deadline date, the Principal Investigator(s) will receive a Notification of Expiration and a copy will be sent to the Care Line Leader/supervisor and Pharmacy, if applicable.

5.5 The research becomes **unapproved** on the expiration date.

5.6 If an accurate and complete progress report is not received by the date indicated in the Notification of Expiration, the research will be suspended or terminated as determined by the IRB.

5.6.1 The Notification of Expiration will request verification that:

5.6.1.1 No subjects are currently enrolled in the research OR

5.6.1.2 Procedures are in place to minimize risks to current subjects when the research is suspended or terminated.

5.6.2 If no subjects are enrolled or if there are no subject safety issues identified, then the IRB will administratively suspend or terminate the research per SOP-003.

5.6.3 If subject safety issues are identified, and the research is suspended by the IRB, the IRB Chair or designee, in consultation with the COS, will determine if continuation of research interventions for enrolled subjects should continue.

5.6.4 If subject safety issues are identified, and the research is terminated by the IRB, the IRB Chair or designee, in consultation with the COS and the sponsor, will determine a course of action for all subjects on the study.

5.6.5 A copy of the IRB decision will be placed in the research file.

5.7 Principal Investigators who are sent a Notification of Expiration become **ineligible** to submit new protocols until an accurate and complete progress report is received by the IRB and all other deficiencies are resolved.

5.7.1 New research submitted by ineligible Principal Investigators will not be reviewed.

5.7.2 Currently approved research is not affected by a Principal Investigator's ineligible status.

5.7.3 The list of ineligible Principal Investigators will be distributed to IRB members with the agenda and included with the meeting minutes.

5.7.4 Principal Investigators will be notified of their ineligible status in the Notification of Expiration.

5.8 The IRB staff checks the progress report for completeness and accuracy, and if applicable, compares it to the previous year’s progress report.

5.8.1 Verify that the consent form, HIPAA authorization, and addendum consent, if applicable, of an active study are the most recently approved versions.

5.8.2 Verify that copies of all signed consent forms, HIPAA authorizations, and addendum consents, if applicable, have been sent to the Research Office within 5 days of enrollment.

5.8.3 Verify that the subject lists for current and previous progress reports are consistent with the approved number for total enrollment.

5.8.4 Verify that the progress report accounts for any serious adverse events of subjects at Stratton VA Medical Center and its affiliates for which the Research Office received written summaries.

5.8.5 Verify that the Research Office received written summaries for any serious adverse events mentioned in the progress report.

5.8.6 Verify that a current copy of the research grant, if applicable, or budget is in the file.

5.8.7 Verify that educational training requirements have been satisfied.

5.9 If any items are missing or questions have been answered unsatisfactorily, a member of the IRB staff will notify the Principal Investigator(s). The IRB staff will not process the paperwork until all corrections have been made.

5.9.1 The IRB and/or IRB staff can use sources other than the Principal Investigator(s) for verification of information in the progress report, such as Data Safety Monitoring Board reports, independent audits, or investigative subcommittees to determine that no material changes have occurred since the previous IRB review.

5.10 An IRB staff member reviews the progress report, and in consultation with the IRB Chair or designee, recommends whether the research qualifies for expedited review or requires full committee review.

5.11 Expedited Review Process:

5.11.1 The IRB Chair or designee cannot have a conflict of interest with the research. If there is a conflict of interest, the vice chair of the IRB, or designee, must assume responsibility for the expedited review.

5.11.2 A progress report qualifies for expedited review if any one of the following items are true:

5.11.2.1 The research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for follow-up of subjects.

5.11.2.2 No subjects have ever been enrolled and no additional risks have been identified.

5.11.2.3 The remaining research activities are limited to data analysis.

5.11.2.4 The research originally qualified for review under expedited review and no additional risks have been identified.

5.11.3 A member of the IRB staff pre-reviews the research. The IRB Chair or designee conducts the review of:

5.11.3.1 The completed progress report form with current consent, HIPAA authorization, protocol education report, and/or addendum consent, if applicable.

5.11.3.2 Adverse events/safety reports/unanticipated problems involving risks to subjects or others received during the reporting period.

5.11.3.3 Withdrawal of subjects from the research or complaints about the research during the reporting period.

5.11.3.4 Summary of recent literature or findings.

5.11.3.5 Amendments or modifications received during the reporting period.

5.11.3.6 Relevant information about risks associated with the research or multicenter trial reports.

5.11.3.7 The current protocol including any modifications.

5.11.3.8 The updated Investigator Brochure, if applicable, received during the reporting period.

5.11.4 The IRB Chair or designee conducting expedited review has the final authority in deciding if continuing review of the research qualifies for expedited review and may recommend full committee review.

5.11.4.1 The primary reviewer is provided with a primary reviewer form to record comments.

5.11.5 If the reviewer finds the research acceptable,

5.11.5.1 The IRB Chair or designee who reviewed the research approves the research.

5.11.5.2 The IRB Chair or designee signs and dates the Expedited Review Continuation Approval letter, indicating the risk level for this reporting period and the new interval of approval.

5.11.5.3 The IRB is notified of the approval in the agenda of the next scheduled IRB meeting.

5.11.5.4 The Expedited Review Continuation Approval letter, and approved stamped consent and HIPAA authorization, if applicable, is sent to the Principal Investigator(s).

5.11.6 The Date of Approval of research approved under expedited review is the date the IRB Chair or designee signs the approval.

5.11.7 If the research is granted approval with modifications:

5.11.7.1 The modifications must be documented in sufficient detail to allow the IRB staff to verify the changes required by the IRB Chair or designee.

5.11.7.2 A Notification of Approval with Contingencies letter, listing all required modifications and conditions for approval, is sent to the Principal Investigator(s).

5.11.7.3 The Principal Investigator(s) responds to the Research Office with a copy of all modified documents within 30 days.

5.11.7.4 The IRB staff reviews the modified documents for confirmation of all modifications required by the IRB.

5.11.7.5 If the submitted documents have not been modified as required, the Principal Investigator(s) is contacted by IRB staff and asked to submit the complete revision as requested.

5.11.7.6 Once the IRB staff determines that the documents contain all required modifications, the IRB Chair or designee signs and dates the Final Continuation Approval letter, indicating the risk level and the interval of approval.

5.11.7.7 If the Principal Investigator(s) does not return the required modified documents within approximately 30 days, the protocol will remain unapproved. At the next scheduled IRB meeting, the IRB will determine whether to suspend or terminate the research per SOP-003.

5.11.7.7.1 If the protocol approval period should expire before the modified documents are reviewed and approved by the IRB Chair or designee, the IRB Chair or designee will notify the Principal Investigator within 2 business days that no new subjects may be enrolled until an approved consent form, HIPAA authorization, or addendum consent ,if applicable, are stamped and approved.

5.11.7.8 A copy of the letter will be placed in the research file.

5.12 Full Committee Review Process:

5.12.1 Progress reports that are recommended for full committee review are placed on the agenda of the monthly IRB meeting and are distributed approximately two weeks in advance of the meeting. The agenda identifies all IRB members who are also participating in the research to alert the committee to a conflict of interest.

5.12.2 All committee members are given a copy of the following items to review:

5.12.2.1 Completed progress report form with current consent form(s), HIPAA authorization, and addendum consent, if applicable.

5.12.2.2 Adverse events/safety reports/unanticipated problems involving risks to subjects or others received during the reporting period.

5.12.2.3 Withdrawal of subjects from the research or complaints about the research during the reporting period.

5.12.2.4 Summary of recent literature or findings.

5.12.2.5 Amendments or modifications received during the reporting period.

5.12.2.6 Relevant information about risks associated with the research or multicenter trial reports.

5.12.3 The IRB staff, with the concurrence of the IRB Chair or designee, assigns two primary reviewers, who are not participating in the research, based on their area of expertise. The IRB Chair or designee is assigned as a 3rd reviewer for all studies.

5.12.4 Primary reviewers are given a copy of the current protocol, including any modifications to the protocol, the protocol education report, and the updated Investigator Brochure received during the reporting period, if applicable. Information distributed to committee members is also given to the primary reviewers, as listed in 5.12.2.

5.12.4.1 Primary reviewers are provided with a primary reviewer form to record their comments.

5.12.5 The continuing review takes place at the monthly meeting of the IRB.

5.12.6 The IRB staff takes minutes at the IRB meeting pertaining to discussion of continuing review of research, and any controverted issues and their resolution.

5.12.7 Minutes are prepared within one week after the meeting and include the attendance of IRB members at the meeting, votes for, against, abstaining, recused, and excused, as well as the recommended period of approval, and if applicable, modifications or other changes to the research.

5.12.8 If the research is approved as submitted,

5.12.8.1 A Final Continuation Approval letter and a copy of the stamped consent(s) and HIPAA authorization, if applicable, are sent to the Principal Investigator(s).

5.12.9 If the research is approved with modifications,

5.12.9.1 A Notification of Approval with Contingencies, listing all required modifications and conditions for approval, is sent to the Principal Investigator(s).

5.12.9.2 The Principal Investigator(s) responds to the Research Office with a copy of all modified documents within 30 days.

5.12.9.3 The IRB staff reviews the modified documents for confirmation of all modifications required by the IRB.

5.12.9.4 If the submitted documents have not been modified as required, the Principal Investigator(s) is contacted by IRB staff and asked to submit the complete revision as requested.

5.12.9.5 Once the IRB staff determines that the documents contain all required modifications, the IRB Chair or designee signs the Final Continuation Approval letter. The letter and a copy of the stamped consent(s) and HIPAA authorization, if applicable, are sent to the Principal Investigator(s).

5.12.9.6 If the Principal Investigator(s) does not return the required modified documents within 30 days, the protocol will remain unapproved. At the next scheduled IRB meeting, the IRB will determine whether to suspend or terminate the research per SOP-003.

5.12.9.6.1 If the protocol approval period should expire before the modified documents are reviewed and approved by the IRB, the IRB Chair or designee will notify the Principal Investigator within 2 business days that no new subjects may be

enrolled until an approved consent form, HIPAA authorization, or addendum consent (if applicable) are stamped and approved.

5.12.9.7 A copy of the letter will be placed in the research file.

5.12.10 The Date of Approval for research approved by the full IRB is the date of the IRB meeting at which the research was approved.

5.12.11 The Date of Expiration is defined as the Date of Approval plus the interval of approval.

5.12.12 If the research is disapproved,

5.12.12.1 Consideration will be given to alternatives that will protect subjects currently enrolled in the research.

5.12.12.2 The IRB Chair will notify the Principal Investigator(s) in the Notification of Disapproval letter of the reasons for disapproval and will offer the Principal Investigator(s) an opportunity to respond in writing to the IRB by a given deadline.

5.12.12.3 If a written response is received by the deadline, the research and disapproval letter are reviewed at the next scheduled meeting of the IRB.

5.12.12.4 If a written response is not received by the deadline or the investigator does not contest the disapproval, the research remains unapproved. At the next scheduled IRB meeting, the IRB will determine whether to suspend or terminate the research per SOP-003.

5.12.12.5 A copy of the letter will be placed in the research file.

5.13 Consents, HIPAA authorization, and assents associated with approved research will be stamped with a Date of Approval and a Date of Expiration. A copy of the stamped consent(s), HIPAA authorization, assent, if applicable, and approval letter, indicating the risk level for the reporting period and the new interval of approval, will be provided to the Principal Investigator(s).

5.13.1 If the educational training requirements have not been completed, the Principal Investigator(s) will be notified that the approval letter and applicable documents will not be released until the requirements are satisfied.

5.14 Copies of all research documents received and sent are filed in the Research Office.

TITLE	**Suspension and Termination of Approved Research by the IRB**	
Document number	**IRB-003**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/14/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to suspend or terminate approved research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious risk or harm to subjects. Written procedures are required for reporting the suspension or termination to the investigator, appropriate institutional officials, and applicable federal agencies and sponsors.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

None

4 REFERENCE DOCUMENTS

45 CFR 46

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 Authority to suspend or terminate research

5.1.1 The IRB may suspend or terminate some or all approved research conducted by a Principal Investigator when:

5.1.1.1 The research is not being conducted in accordance with IRB requirements; or

5.1.1.2 The research is associated with unexpected serious risk or harm to subjects; or

5.1.1.3 The IRB finds reasonable cause to remove the Principal Investigator from the study; or

5.1.1.4 There is an investigation as to whether research should be terminated or suspended, and there is reasonable concern that subjects are at increased risk pending the outcome of the investigation.

5.1.2 The IRB Chair or designee may temporarily suspend some or all approved research conducted by a Principal Investigator when:

5.1.2.1 There is reasonable concern that subjects are at increased risk and there is inadequate time for convening an IRB meeting to determine if a suspension should take place.

5.1.3 If the IRB Chair or designee suspends or terminates any approved research:

5.1.3.1 The research will be placed on the agenda of the next scheduled IRB meeting.

5.1.3.2 The IRB will approve, modify or reverse the suspension or termination.

5.2 Subject protection after suspension or termination

5.2.1 If approved research is suspended or terminated, the IRB will consider alternatives that protect subjects currently enrolled in the research.

5.2.2 When required for subject safety, the IRB Chair or designee will directly notify Principal Investigator(s) of suspension or termination of approved research. If the Principal Investigator is unavailable, the IRB Chair or designee will directly notify the Care Line Leader and institutional officials about the suspension or termination of approved research.

5.2.3 Once notified of the suspension, the investigator must immediately submit to the IRB Chair or designee a list of research subjects for whom suspension of the research would potentially cause harm. The IRB Chair or designee, in consultation with the Chief of Staff (COS), will determine if the subjects may continue in the research.

5.2.3.1 In the absence of the Principal Investigator, the IRB Chair or designee, in consultation with the ACOS R&D, will determine an appropriate qualified interim individual to assume the responsibilities of the study.

5.2.5 If the Principal Investigator does not respond to the IRB request by the deadline indicated, the IRB Chair or designee will contact

the Care Line Leader and, if appropriate, institutional officials to determine if the subjects may continue in the research.

5.3 Reporting of suspension or termination

5.3.1 The IRB staff will send to Principal Investigators a written notification of suspended or terminated research within 5 business days of the decision.

5.3.1.1 The reasons for the suspension or termination will be included in the notification.

5.3.1.2 For suspended research, enrollment of new subjects cannot occur. The IRB, or IRB Chair or designee, in consultation with the COS, will determine if continuation of research interventions for enrolled subjects should continue.

5.3.1.3 A copy of the notification will be sent to the Care Line Leader and appropriate institutional officials, such as the Medical Center Director, the Chief of Staff, Research Compliance Officer, and the Research and Development Committee.

5.3.2 If the DHHS regulates the research, the IRB Chair or designee will forward a copy of the notification to OHRP within 10 business days of the decision.

5.3.3 If the FDA regulates the research, the IRB Chair or designee will forward a copy of the notification to the FDA within 10 business days of the decision.

5.3.4 The IRB Chair or designee will forward a copy of the notification to Office of Research Oversight (ORO) and the Research Compliance Officer within 10 business days of the decision.

5.3.5 If a federal agency other than FDA or OHRP funded the research, the IRB Chair or designee will forward a copy of the notification to the applicable federal agency within 10 business days of the decision.

5.3.6 If a sponsor other than a federal agency funded the research, the IRB Chair or designee will forward a copy of the notification to the sponsor within 10 business days of the decision.

5.4 Removal of suspension

5.4.1 The investigator will submit a written response to the IRB within 30 days of the date of the suspension letter. In the response, the investigator must provide justification for the removal of the suspension.

5.4.2 The letter of justification will be reviewed at the next scheduled IRB meeting. The IRB will make a determination to lift the suspension, maintain the suspension with conditions, or terminate the study.

5.4.3 IRB review and re-approval must occur prior to re-initiation of the research.

5.5 Administrative suspension or termination

5.5.1 If approved research is suspended or terminated by the IRB due to, for example, failure to submit/incomplete progress report submissions, copies of the notification will be sent to the Care Line Leader and appropriate institutional officials.

5.5.1.1 If an investigator repeatedly fails to submit/complete progress reports, the continuous non-compliance with IRB requirements would be reported to the appropriate agencies as in 5.3.

5.6 Records

5.6.1 The date the approved research is suspended or terminated by the IRB is recorded in the database.

5.6.2 The file is removed from the active files to be processed for termination by R&D. The file is then labeled as terminated and stored for at least three years after termination.

TITLE	**Closure of Research by an Investigator**	
Document number	**IRB-004**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/14/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required for investigator - initiated closure of research.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Protocol Progress Report Form

Notification of Closure

4 REFERENCE DOCUMENTS

45 CFR 46

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 Closure of a research protocol requires a completed Protocol Progress Report Form with a request for closure by the Principal Investigator(s).

5.2 If a Principal Investigator(s) requests closure of a protocol and has not submitted a completed Protocol Progress Report Form with a request for closure, the IRB staff provides a Protocol Progress Report Form to the Principal Investigator(s).

5.3 The Principal Investigator(s) is expected to complete the progress report form and provide all applicable attachments requested on the form.

5.4 Upon receipt of a progress report from a Principal Investigator(s) requesting closure, the IRB staff stamps it with the date of receipt and enters the request into the database.

5.5 The IRB staff checks the progress report for completeness and accuracy.

5.6 The IRB staff compares the progress report with previous progress reports.

5.6.1 Verify that the subject lists for current and previous progress reports are consistent with the approved number for total enrollment.

5.6.2 Verify that the progress report accounts for any serious adverse events of subjects at Stratton VA Medical Center and its affiliates for which the Research Office received written summaries.

5.6.3 Verify that the Research Office received written summaries for any serious adverse events mentioned in the progress report.

5.7 If any items are missing or questions have been answered unsatisfactorily, a member of the IRB staff will notify the Principal Investigator(s). The IRB staff will not process the paperwork until corrections have been made.

5.7.1 The IRB and/or IRB staff can use sources other than the Principal Investigator(s) for verification of information in the progress report, such as Data Safety Monitoring Board reports, independent audits, or investigative subcommittees to determine that no material changes have occurred since the previous IRB review.

5.8 If requests for additional information are inadequate or additional requested items are still missing, then the protocol is sent to the full committee for review of the closure and recommended action on the inadequate information or missing items.

5.9 Once the progress report is complete, the IRB Chair or designee reviews the request for closure, and signs the Notification of Closure letter. The date that the Notification of Closure letter is signed is the date of closure.

5.10 The Notification of Closure letter is sent to the Principal Investigator(s) and a copy is put in the file.

5.11 The closure of the protocol is listed in the agenda of the next scheduled IRB meeting.

5.12 The date the research is closed by the IRB is recorded in the database. The file is removed from the active files to be processed for closure by R&D. The file is then labeled as closed and stored for at least three years after closure.

5.13 Principal Investigator(s) may reopen research they have closed by following the procedures for initial review of research.

TITLE	**Research Involving Adults Who Lack Capacity to Provide Informed Consent**	
Document number	**IRB-005**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/14/2004**

INR 6C

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to guide the IRB in the review of research involving adults who lack the capacity to provide informed consent.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

None

4 REFERENCE DOCUMENTS

45 CFR 46
21 CFR 50, 56
38 CFR 16
VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research
ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 **Research not involving greater than minimal risk:** The IRB may approve research involving adults who lack capacity to provide informed consent and not involving greater than minimal risk, provided that the IRB finds and documents that:

5.1.1 The objectives of a trial cannot be met by means of a trial involving subjects who can give informed consent personally.

5.1.2 No greater than minimal risk.

5.1.3 Adequate provisions are made for soliciting the assent of the subject and the consent of the subject's legally authorized representative.

5.2 **Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects:** The IRB may approve research involving adults who lack capacity to provide informed consent and involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects, provided that the IRB finds and documents that:

5.2.1 The objectives of a trial cannot be met by means of a trial involving subjects who can give informed consent personally;

5.2.2 More than minimal risk is presented to the subjects;

5.2.3 The research holds out the prospect of direct benefit for the individual subject or is likely to contribute to the subject's well-being;

5.2.4 The risk is justified by the anticipated benefit to the subjects;

5.2.5 The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and

5.2.6 Adequate provisions are made for soliciting the assent of the subject and the consent of the subject's legally authorized representative.

5.3 **Research involving greater than minimal risk and no prospect of direct benefit to the individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition:** The IRB may approve research involving adults who lack capacity to provide informed consent and that may involve more than minimal risk by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure which is not likely to contribute to the well-being of the subject, only if the IRB finds and documents that:

5.3.1 The objectives of a trial cannot be met by means of a trial involving subjects who can give informed consent personally;

5.3.2 The risk represents a minor increase over minimal risk;

5.3.3 The intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;

5.3.4 The intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of disorder, or condition; and

5.3.5 Adequate provisions are made for soliciting the assent of the subject and the consent of the subject's legally authorized representative.

5.4 **Waiver of assent:** The IRB may waive the requirement for assent of the subject when:

5.4.1 The capability of some or all of the subjects is so limited that they cannot reasonably be consulted;

5.4.1.1 In determining whether subjects are capable of assent, the IRB shall take into account the psychological state and physical state of the subjects involved.

5.4.1.2 This judgment may be made for all subjects to be involved in research under a particular protocol, or for each subject, as the IRB deems appropriate.

5.4.2 The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the subject and is available only in the context of the research; or

5.4.3 IRB determines that the assent may be waived according to the same criteria by which consent may be waived.

5.5 The IRB may waive some or all of the requirements for informed consent or may waive the requirement for documentation of informed consent (see Informed Consent SOP).

5.6 Consent of the legally authorized representative shall be documented in accordance with the Informed Consent SOP.

5.7 A subject's capacity to consent to research must be assessed prior to consenting and continually assessed while the subject is in the research. If subjects enrolled in the research develop the capacity to provide informed consent, the IRB may require consent of the subject in accordance with the Informed Consent SOP.

5.8 When the IRB determines that assent is required, assent shall be documented by having the subject sign and personally date the assent.

TITLE	**Revisions to Previously Approved Research**	
Document number	**IRB-006**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 02/05/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to document review of changes to IRB approved research and to report the IRB's actions to the Principal Investigator(s).

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Protocol Review Request Form for Revision/Amendment
Request for Change in Principal Investigator
Request for Change in Co-investigator/Sub-investigator
Primary Reviewer Form
Notification of Approval with Contingencies
Expedited Review Revision/Amendment Approval letter
Full Committee Final Revision/Amendment Approval letter
Notification of Disapproval letter

4 REFERENCE DOCUMENTS

45 CFR
21 CFR 50, 56
38 CFR 16
VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research
ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 Principal Investigators may request review of a revision to previously approved research by submitting a Protocol Review Request Form for Revision/Amendment with a copy of all revised documents.

5.1.1 If the amendment addresses an issue related to biosafety, animals, or radiation safety, the appropriate committee or subcommittee must first approve the amendment.

5.2 Upon receipt of the revision request, the IRB staff stamps it with a date of receipt. The information is reviewed for completeness and accuracy by the IRB staff and is entered into the database.

5.3 If any items are missing or there are questions about the revision, the Principal Investigator(s) or the designated contact person may be contacted by the IRB staff and requested to provide additional information or documents.

5.4 Revisions that represent a minor change may be reviewed by expedited review or may be reviewed by the full IRB. All other changes must be reviewed by the full IRB.

5.4.1 Revisions are minor if the changes do not result in an increase in risk of greater than minimal risk.

5.4.2 The HRPP Coordinator reviews the request, and in consultation with the IRB Chair or designee, recommends whether the research qualifies for expedited review or requires full committee review.

5.5 Expedited Review Process:

5.5.1 A member of the IRB Staff pre-reviews the research. The IRB Chair or designee conducts the review of the revision.

5.5.2 The IRB Chair or designee conducting expedited review has the final authority in deciding whether the revision qualifies for expedited review and may recommend full committee review.

5.5.3 In order to approve revisions covered by this policy, the reviewer shall determine that criteria for approval of research are satisfied as per 38 CFR 16.110 and 16.111.

5.5.4 If the reviewer requests changes or additional information, the IRB staff contacts the Principal Investigator(s) or the designated contact person and requests the information. Upon receipt of the requested information, the changes or additional information are forwarded to the reviewer.

5.5.5 If the reviewer still cannot approve the revision as submitted, the Principal Investigator(s) or designated contact person is notified. The Principal Investigator(s) may modify the research for resubmission to the IRB or resubmit the research for review at a full IRB meeting.

5.5.6 If the reviewer recommends full committee review, the Principal Investigator(s) or designated contact person is notified that the revision must be reviewed by the full committee and is asked to provide additional copies of the research submission.

5.5.7 The reviewer may not disapprove revisions under Expedited Review.

5.5.8 If the reviewer finds the revision acceptable:

5.5.8.1 The IRB Chair or designee who reviewed the revision approves the revision.

5.5.8.2 The IRB Chair or designee signs and dates the Expedited Review Revision/Amendment Approval letter. This date is the approval date.

5.5.8.3 The Expedited Review Revision/Amendment Approval letter, and approved stamped consent(s), HIPAA authorizations, and assent, if applicable, are sent to the Principal Investigator(s). A brief description of the revision is included in a parenthetical after the protocol title in the Expedited Review Revision/Amendment Approval letter.

5.5.8.4 The IRB is notified of the approval of the revision in a brief summary in the agenda of the next scheduled IRB meeting.

5.5.8.5 The expiration date of the research remains the same as that of the most recent version approved by the IRB.

5.6 Full Committee Review Process:

5.6.1 Revisions that require full committee review are placed on the agenda of the monthly IRB meeting. The revision is summarized on the agenda and the agenda identifies all IRB members who are participating in the research to alert the committee to a conflict of interest.

5.6.2 The IRB staff, with the concurrence of the IRB Chair or designee, assigns two primary reviewers, who are not participating in the research, based on their area of expertise. The IRB Chair or designee is assigned as a 3rd reviewer for all studies.

5.6.2.1 The primary reviewers may not be principal investigators, sub-investigators, or co-investigators of research they are reviewing.

5.6.2.2 The primary reviewers are given a copy of the Protocol Review Request Form for Revision/Amendment, revised or addendum pages from the protocol, and if applicable, revised consent and HIPAA authorization documents, and/or the Investigator Brochure with a summary list of Investigator Brochure changes.

5.6.2.3 Committee Members are given a copy of the revision to review. The revision typically consists of a Protocol Review Request Form for Revision/Amendment, revised or addendum pages from the protocol, and if applicable, revised consent and HIPAA authorization documents and/or a summary list of Investigator Brochure changes. All materials are distributed to committee members approximately two weeks in advance of the meeting.

5.6.2.4 Primary reviewers are provided with a Primary Reviewer Form to record their comments.

5.6.3 The review of revisions takes place at the monthly meeting of the IRB.

5.6.4 The IRB staff takes minutes at the IRB meeting pertaining to discussion of the revision.

5.6.5 Minutes are prepared within one week after the meeting and include:

5.6.5.1 Attendance of IRB members at the meeting.

5.6.5.2 The votes for, against, abstaining, recused, and excused. IRB members with a conflicting interest must recuse themselves from voting.

5.6.5.3 Modifications or any other changes to the research required by the IRB.

5.6.5.4 The basis for requiring changes in or disapproving research.

5.6.5.5 A written summary of any discussion of controverted issues and their resolution.

5.6.6 If the revision is approved as submitted,

5.6.6.1 The IRB Chair or designee signs the Final Revision/Amendment Approval letter.

5.6.6.1.1 The Date of Approval is the date of the meeting at which the revision(s) was approved.

5.6.6.2 The Final Revision/Amendment Approval letter is sent to the Principal Investigator(s) and a copy is sent to the R&D Committee and applicable personnel (i.e. Pharmacy).

5.6.7 If the revision is approved with modifications,

5.6.7.1 The modifications must be documented in sufficient detail to allow the IRB staff to verify the changes required by the IRB.

5.6.7.2 A Notification of Approval with Contingencies, listing all required modifications and conditions for approval, is sent to the Principal Investigator(s).

5.6.7.3 The Principal Investigator responds to the Research Office with a copy of all modified documents within 30 days.

5.6.7.4 The IRB staff reviews the modified documents for confirmation of all modifications required by the IRB.

5.6.7.5 If the submitted documents have not been modified as required, the Principal Investigator(s) is contacted by IRB staff and asked to submit the complete revision as requested.

5.6.7.6 Once the IRB staff determines that the documents contain all required modifications, the IRB Chair or designee signs the Final Revision/Amendment Approval letter.

5.6.7.7 The Final Revision/Amendment Approval letter is sent to the Principal Investigator(s) and a copy is sent to the R&D Committee and applicable personnel (i.e. Pharmacy).

5.6.7.8 If the Principal Investigator(s) does not return the required modified documents within approximately 30 days from the date the letter was issued, the IRB staff notifies the IRB Chair or designee to determine a course of action.

5.6.8 If the revision is disapproved, the IRB staff notifies the Principal Investigator(s) in the Notification of Disapproval letter of the reasons for disapproval and offers the Principal Investigator(s) an opportunity to resubmit the revision to the IRB.

5.7 Revised consents, HIPAA authorizations, and assents associated with modifications are stamped with a Date of Approval and a Date of Expiration. A copy of the stamped consent(s), HIPAA authorizations, and assent will be provided to the investigator.

5.7.1 The Date of Approval is defined as the date of the meeting at which the revision was approved.

5.7.2 The Date of Expiration remains unchanged from the original approval, unless a more recent version of the revised document was approved by the IRB.

5.8 The revisions and copies of documents received and sent are filed in the Research Office.

5.9 The IRB staff files the Primary Reviewer Form with the revision/amendment submission.

TITLE	**Record Keeping for the IRB**	
Document number	**IRB-007**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 04/21/2004**

IRB:5B;C;D; INR 1E

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to detail maintenance of adequate documentation of IRB activities.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

New Protocol Submission Form
Protocol Review Request Form for Revision/Amendment
Request for Change in Co-investigator/Sub-investigator
Request for Change in Principal Investigator
Primary Reviewer Form
Notification of Approval with Contingencies
Expedited Review Final New Protocol Approval letter
Full Committee Final New Protocol Approval letter
Continuation Approval letter
Review of Subcommittee on Human Studies (VA Form 10-1223)
Notification of Disapproval letter
Non-Exempt Protocol Progress Report Form
Exempt Protocol Progress Report Form
Expedited Review Revision/Amendment Approval letter
Full Committee Revision/Amendment Approval letter
New Protocol Submission Checklist
Notification of Expiration letter
Notification of Closure letter
Adverse Event (AE) Reporting Form
HIPAA Authorization
Waiver of HIPAA Authorization

4 REFERENCE DOCUMENTS

45 CFR
21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 New Protocols Reviewed and Approved by the Full Committee

5.1.1 Before the monthly IRB meeting, the IRB staff prepares files for new protocol submissions. Each new protocol file consists of a New Protocol Review Request Form, budget and accounting documents, and any supporting documents submitted by a Principal Investigator(s).

5.1.2 After the minutes are signed following the IRB meeting at which a new protocol was reviewed and approved, the new protocol file is placed in the *pending* file cabinet until all required modified documents have been submitted to the Research Office by the Principal Investigator(s).

5.1.3 When the Full Committee Final New Protocol Approval letter is issued, the protocol file is filed in the R&D *pending* file cabinet with a copy of the Full Committee Final New Protocol Approval letter, a copy of the original approved stamped consent and HIPAA document(s), if applicable, scientific evaluations, if any, and any other approved supporting documents.

5.2 New Protocols Reviewed and Approved under Expedited Review

5.2.1 IRB staff prepares files for new protocols approved under Expedited Review. Each new protocol file consists of a New Protocol Review Request Form, budget and accounting documents, and copies of all supporting documents submitted by a Principal Investigator(s).

5.2.2 When the Expedited Review Final New Protocol Approval letter is issued, the protocol file is filed in the R&D *pending* file cabinet with a copy of the Expedited Review Final New Protocol Approval letter, a copy of the original approved stamped consent and HIPAA document(s), if applicable, and any other approved supporting documents.

5.3 Revisions Reviewed and Approved by the Full Committee

5.3.1 After the minutes are signed following the IRB meeting at which a revision was reviewed and approved, protocol files are placed in the *pending* file cabinet until the Principal Investigator(s) submits any required modified documents.

5.3.2 When the Full Committee Final Revision/Amendment Approval letter is issued, the protocol file is filed in the *active* file cabinet with a copy of the Full Committee Final Revision/Amendment Approval letter, the Protocol Review Request Form for Revision/Amendment, a copy of the approved revised stamped consent and HIPAA document(s), if applicable, and any other approved documents.

5.4 Revisions Reviewed and Approved under Expedited Review

5.4.1 When the Expedited Review Revision/Amendment Approval letter is issued, a copy of the Expedited Review Revision/Amendment Approval letter with the Protocol Review Request Form for Revision/Amendment, the approved revised stamped consent and HIPAA document(s), if applicable, and any other approved supporting documents are filed in the protocol file in the *active* file cabinets.

5.5 Adverse Event (AE) Reporting Forms that have been processed are filed in the protocol file.

5.6 Significant deviations that have been reported to the IRB are filed in the protocol file.

5.7 All reviewed correspondence between a Principal Investigator or designated contact person and the IRB is filed in the protocol file.

5.8 Significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, are filed in the protocol file.

5.9 All progress reports and any attachments received are filed in the protocol files.

5.9.1 If the research is approved for continuation, a Continuation Approval letter and a copy of the approved stamped consent and HIPAA document(s), if applicable, are filed in the protocol file. If applicable, a Notification of Approval with Contingencies letter and required modified documents are also filed in the protocol file.

5.9.2 If the research is disapproved for continuation, a Notification of Disapproval letter is filed in the protocol file.

5.10 Disapproved Protocols

5.10.1 Files of new research disapproved by the IRB are held in the Research Office. A Notification of Disapproval letter is placed in the protocol file.

5.10.1.1 If a Principal Investigator resubmits the protocol, the modified protocol submission is filed in the original protocol file.

5.10.1.2 If a Principal Investigator does not resubmit the protocol within approximately 3 months, IRB staff may destroy the contents of the protocol file.

5.11 Closed Protocols

5.11.1 When a Notification of Closure is issued, the closed protocol file is forwarded to the R&D Committee for final closure. The file is then removed from the Research Office filing system and archived outside the Research Office in a secure location within the institution.

5.11.2 The VA study files shall be retained for at least 5 years, and IND study files shall be retained for 10 years.

5.12 Minutes of IRB meetings are kept in the Research Office for at least three years.

5.12.1 Copies of all approved IRB minutes are forwarded to the R&D Committee for review and approval.

5.13 Educational training records are kept in the Research Office for at least 3 years.

5.14 A list of current IRB members is maintained on the P drive and the VISN 2 Research website by the Research Office and is updated as changes occur.

5.14.1 IRB staff maintains a file of the curricula vitae of current IRB members that is updated annually.

5.15 A master file of the original IRB Standard Operating Procedure (SOP) is kept in the Research Office.

5.16 Requests for access to IRB records by VA representatives or other federal agencies must be made through the Research Administration Office at reasonable times and in a reasonable manner. Copies of IRB records will be granted only with proper approval. Each individual seeking access must document access in the IRB “Access Log to Research Office Files”. The log is maintained by the HRPP Coordinator and includes the date, name, file accessed, and reason for access.

5.17 Records that pertain to clinical investigations regulated by the Food & Drug Administration (FDA) will be accessible for inspection and copying by authorized representatives of the FDA at reasonable times and in a reasonable manner.

INR 1E

5.18 The electronic database system tracks all events related to the research, such as initial review, continuation review, AE’s, as well as the documents submitted that are related to the events.

TITLE	**Processing of Adverse Event, Injury and Unanticipated Problem Reports**	
Document number	**IRB-008**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/12/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required for processing reports of adverse events.

The IRB's policy requires the Principal Investigator to report to the IRB within 5 business days of becoming aware of any serious adverse event that occurs in association with a research study in which there is harm (including physical, legal, social, economic or psychological harm or injury) or other unanticipated problems involving risks to research subjects and others. Such events include:

- Significant change in the risk/benefit relationship of a research study as originally presented in the protocol and approved by the IRB.
- Serious and unexpected adverse event.
- Death occurring on study or within 30 days of the last study intervention, regardless of whether the death was related to the study.
- Any event that requires prompt or urgent reporting to the sponsor.

All other Adverse Events (serious and non-serious, expected and unexpected) will be reported at the time of continuation review.

The IRB considers failure to follow this policy to be non-compliance.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Adverse Event (AE) Reporting Form

IRB-003 "Suspension and Closure of Approved Research by the IRB."

4 REFERENCE DOCUMENTS

45 CFR 46

21 CFR 50, 56

21 CFR 312, 812

38 CFR 16

VHA Handbook 1058.1 Reporting Adverse Events in Research to the Office of Research Oversight

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 If a Principal Investigator contacts the Research Office regarding an adverse event, the IRB staff obtains the available pertinent information (Principal Investigator's name, protocol title, date of the adverse event, subject initials, description of the event, relationship to study, person spoken with). The recorded information is retained until an Adverse Event (AE) Reporting Form and any attachments are received from the Principal Investigator.

5.1.1 If documentation has not been received for a phone report within 5 business days, the IRB staff contacts the Principal Investigator or contact person to obtain a written report.

5.2 The Principal Investigator, based on provisions in the protocol for monitoring and reporting data collected to ensure subject safety, determines the relatedness of an on-site/off-site AE to the research. These provisions may include a Data Safety Monitoring Board and a plan for reporting DSMB findings to the IRB.

5.3 Upon receipt of an Adverse Event (AE) Reporting Form from a Principal Investigator, the Research Office staff stamps it with a date of receipt and checks the form for completeness.

5.4 If any applicable sections of the Adverse Event (AE) Reporting Form are incomplete or have been answered unsatisfactorily, the IRB staff will return the form and any attachments to the Principal Investigator with a written explanation and a deadline for response. A copy of the form is kept with the IRB records until the original is returned.

5.4.1 At the discretion of the IRB staff, the Principal Investigator or the designated contact person may be contacted to make the corrections in the Research Office instead of returning the Adverse Event (AE) Reporting Form to the Principal Investigator.

5.4.2 The IRB Staff will track the Adverse Event (AE) Reporting Forms returned to the Principal Investigator and their response.

5.5 The IRB Chair or designee will review all of the adverse event reports to determine whether any revisions or substantive actions are required and if so, will refer the adverse event to the full IRB to review and determine the actions required. All on-site AE's are reviewed by the full committee. Such actions include, for example, modification of the consent document, an addendum consent, modification of the protocol, change in investigator status, or possible suspension or termination of the research.

5.5.1 If the report indicates an unanticipated problem involving risks to subjects or others, then the IRB Chair or designee reports the event to the FDA, OHRP, ORO, sponsor, and institutional officials, as appropriate.

5.5.1.2 Reports to ORO should be submitted as indicated in Appendix A of VHA Handbook 1058.1.

5.5.2 The IRB Chair or designee documents the recommended change on the Adverse Event (AE) Reporting Form or documents that no actions are required, and signs and dates the form.

5.6 If the IRB Chair or designee or the full IRB request any modification to the consent document or research protocol, or addendum consent, the IRB Chair or designee will communicate to the Principal Investigator the requirement to submit the modifications to the IRB for review. If the IRB does not receive the complete modification or a satisfactory explanation as to why the modification could not be completed within four weeks,

5.6.1 The Principal Investigator is sent a Notification indicating failure to comply with a request for modification. A copy will be sent to the Care Line Leader and the institutional official.

5.6.2 The research is suspended following IRB-003 “Suspension and Termination of Approved Research by the IRB.”

5.6.3 The Principal Investigator becomes ineligible to submit new research.

5.6.4 The Principal Investigator remains ineligible until a complete modification is received by the IRB and all other deficiencies are resolved.

5.6.5 The list of ineligible Principal Investigators will be distributed to IRB members with the agenda and included with the meeting minutes.

5.7 If the IRB Chair or designee or the full IRB determines that an on-site adverse event requires reporting, then

5.7.1 The IRB staff prepares a report of the event and corrective actions to be taken.

5.7.2 The IRB staff sends a copy of the report signed by the IRB Chair or designee to the Care Line Leader and the institutional official.

5.7.3 A copy of the report is included with the agenda for the next scheduled IRB meeting.

5.7.4 The IRB staff forwards a copy of the notification to Office for Human Research Protections (OHRP) and Office for Research

Oversight (ORO) within 10 working days of the IRB's determination.

5.7.4.1 An unexpected death of a research subject, as determined by the IRB, should be reported by the institutional official or designee to ORO no later than 24 hours after the IRB is informed of the death.

5.7.4.1.1 If the IRB is unable to determine whether a research subject's death was unexpected after 10 working days of being informed of the death, the death must then be reported to ORO.

5.7.4.1.2 When a final determination is made as to whether or not the death was unexpected, a follow-up report must be made to ORO.

5.7.5 If a federal agency funded the research, the IRB staff forwards a copy of the notification to the applicable federal agency.

5.7.6 If a sponsor other than a federal agency funded the research, the IRB staff forwards a copy of the notification to the sponsor.

5.8 If an ON-SITE AE has occurred for a study that is closed locally, and the drug is currently approved for use by the FDA,

5.8.1 the investigator should file a Med Watch 3500 form with the FDA and the sponsor, and include the name of the protocol in which the subject was participating.

5.8.2 the information should be submitted to the IRB for review and approval, and does not require reopening the study unless otherwise indicated by the IRB.

5.9 If an OFF-SITE AE has occurred for a study that is closed locally, the investigator should submit the AE to the IRB for review and approval, and does not require reopening the study unless otherwise indicated by the IRB.

5.10 Adverse Event (AE) Reporting Forms and any attachments are filed in the Research Office. Informed consent copies attached to the AE Reporting Form are destroyed once the form is reviewed and signed by the designated reviewer.

5.11 Reports for AE's in research or the imminent threat thereof should be accompanied by a copy of all IRB minutes from meetings in which the AE in research and subsequent actions were discussed, ratified, or summarized.

TITLE	**Conflict of Interest**	
Document number	**IRB-009**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 01/22/2004**

INR 3A&B

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Conflicts of interest have increased as the relationships of investigators with private corporations, pharmaceutical companies, and outside institutions have become more complex. Written procedures are required for conflict of interest in research.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Financial Conflict of Disclosure

4 REFERENCE DOCUMENTS

VHA Handbook 1200.13 Conflict of Interest in Research

5 PROCEDURE

5.1 All initial human subject research proposals submitted to the Stratton VA must contain a Stratton VA Medical Center "Financial Conflict of Disclosure" Form for each member of the research team.

5.1.1 If the form(s) is missing or information is incomplete, the IRB staff will contact the Principal Investigator to submit the form(s) or the missing information. Final approval for the research will not be issued until the document is completely reviewed and approved by all appropriate signatory officials.

5.2 The ACOS/R conducts a preliminary review of the disclosure statement(s). If satisfied, the ACOS/R approves the disclosure statement(s).

5.2.1 The ACOS/R contacts the research team member if there are questions concerning the information in the disclosure.

5.3 The Conflict of Interest (COI) Administrator, appointed by the Medical Center Director, reviews the financial disclosure statement from each

member of the research team, and with consultation from the network Research Compliance Officer will:

5.3.1 determine whether there is an actual or potential conflict of interest that could impact an investigator's proposed or current research. The conflict may affect the design, conduct, or reporting of the research.

5.3.2 determine, with the assistance of VA regional counsel, what conditions or restrictions, if any, should be imposed to manage, reduce, or eliminate the conflict.

5.3.3 report findings and identify steps to manage the conflict of interest to the appropriate institutional official, the IRB, the R&D Committee, and the research team member.

5.3.4 establish, with the assistance of VA regional counsel a process to allow the research team member to appeal a decision restricting the conduct of research and requiring specific steps to manage, reduce, or eliminate the conflict of interest.

5.3.5 establish criteria for evaluating a research team member's appeal.

5.3.5.1 Criteria may include the nature of the research, the unique experience or qualifications required to conduct the research, the number of other investigators that may possess these qualifications, the nature and magnitude of the conflict of interest, as well as any substantial effect of the research on the conflict of interest such as increasing financial gains for the investigator.

5.4 The Conflict of Interest Administrator will maintain records of all financial disclosures and all actions taken by the medical center with respect to each conflicting interest for the period that the protocol records are maintained.

5.5 The IRB is responsible for identifying, reviewing, and requiring appropriate changes in protocols affected by COI for research involving human subjects.

5.5.1 The IRB may determine that, based on the actions and recommendations of the COI Administrator and the research team member's Financial COI Disclosure statement, that the research protocol should not be conducted at the institution.

5.5.1.1 The IRB should be aware of the funding arrangements and determine if the protocol addresses any COI and the management of the COI.

5.5.1.2 The IRB may determine that the Principal Investigator must disclose to the research subject financial arrangements with the research sponsor.

5.5.1.3 The disclosure to the subjects may be in discussion in the consent regarding the source of funding, the payment arrangements for the Principal investigator, the nature of the COI, how the COI is being managed, and the additional protections that have been put in place.

5.5.1.3.1 The additional protections may include special measures to modify the consent process, having a non-biased third party obtain the consent, and recruit subjects, or having the investigator recuse him or herself from decision making that may influence the outcome or reporting of the research results.

5.5.1.4 At the time of initial or continuing review of research, the IRB will consider the impact of the COI on the subject, the risk to the subject, the subject's willingness to participate in the research after disclosure of the conflict, and the impact on the research and the research results.

5.5.1.5 The IRB will determine if actions in addition to those required by the COI Administrator, should be taken to manage, reduce, or eliminate the COI.

5.6 The Research & Development (R&D) Committee is responsible for reviewing the actions taken by the IRB, and may approve the IRB's actions and add other stipulations or changes to the proposal, but may not disallow any of the IRB's stipulations or required changes regarding the COI.

5.7 The R&D Committee is also responsible for issues involving conflict of interest for studies not involving humans. The committee shall determine what actions in addition to those required by the COI Administrator, should be taken by the institution or the investigator to manage, reduce, or eliminate the COI.

5.8 IRB and R&D members must recuse themselves from review of protocols for which the conflict exists.

5.9 The conflict of interest findings of the COI Administrator, IRB, and R&D are reported to the research team member and the Medical Center Director.

5.9.1 The Medical Center Director may add to the stipulations or requirements but may not lessen them.

5.9.2 In situations where the COI cannot be resolved, the Medical Center Director will make the final binding decision regarding the COI.

5.10 Any member of the research team may appeal the recommendations of the COI Administrator, IRB and/or R&D Committees in accordance with VA and medical center policies and procedures.

5.11 The research team member must comply with the final decision of the Medical Center Director in managing the COI.

5.12 The medical center may take the following actions to manage, reduce, or eliminate COI:

5.12.1 Public disclosure of significant financial interests;

5.12.2 Monitoring of research by independent reviewers;

5.12.3 Modification of the research plan and/or the informed consent documents;

5.12.4 Disqualification from participation in all or a portion of the research;

5.12.5 Divestiture of significant financial interests; or

5.12.6 Severance of relationships that create actual or potential conflicts.

5.13 If a COI is identified after a research protocol has been approved or initiated, the COI Administrator, along with the IRB and R&D, will identify the impact of the conflict on the protocol and the research subjects, if applicable, and corrective actions to be taken to decrease the impact. Corrective actions may include:

5.13.1 Modifying the protocol and consent;

5.13.2 Reconsenting subjects or removing the research team member from a role in subject selection;

5.13.3 Supervision of the protocol by independent reviewers; and/or

5.13.4 Requiring that the COI must be disclosed in all publications or presentation resulting from the research.

5.14 When a significant COI exists and cannot be eliminated (as indicated in 5.13), the consent form must contain a discussion of the financial arrangement, and how the conflict of interest is being managed and the additional protections that have been put in place. The inability to resolve a significant COI will be reported to the Medical Center Director through the appropriate committees.

5.15 If a research team member fails to comply with the COI policy or with corrective actions, the COI Administrator will report the failure to comply to the Medical Center Director and this failure may result in the following conditions or restrictions:

5.15.1 Termination of the research protocol;

5.15.2 Removal of the investigator from the research team; or

5.15.3 Revocation of the privilege to conduct research within the VA.

5.16 The research team member may also be sanctioned by the Public Health Service, Food and Drug Administration, or other applicable entities depending on the seriousness of the non-compliance and the determination of the research sponsor.

TITLE	**Informed Consent**	
Document number	**IRB-010**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 04/08/2004**

INR 6C&D

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to guide the IRB in the review of informed consent.

The IRB requires that all consent documents follow the Stratton VA IRB Consent Template to ensure that all required basic elements of information and appropriate additional elements of consent are present in the consent document as set forth in VA and other federal regulations. Consent forms must be approved by the IRB and signed by the subject or the subject's legally authorized representative, except in cases where documentation of informed consent is waived by the IRB. Exceptions are allowed on a case-by-case basis. The consent should be written at an 8th grade reading level and must be on the VA Form 10-1086.

Unless informed consent has been waived by the IRB, the investigator must obtain consent prior to enrolling a subject into a study or conducting any study procedures required by the protocol. The consent document must be signed and personally dated by the subject or by the subject's legally authorized representative, and by the person who conducted the informed consent discussion. The IRB or its designee has the authority to observe the consent process. A subject's capacity to consent to research must be assessed prior to consenting and continually assessed while the subject is in the research study. Before participation in the trial, the subject or the subject's legally authorized representative, as defined in the Informed Consent Training Packet, must be given a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally authorized representative must be given a copy of the signed and dated consent form updates and a copy of any amendments to the written information originally provided.

Consent must be obtained without coercion or undue influence and must be communicated to prospective subjects or their legally authorized representative in a language that is understandable to the subject or representative. The

prospective subject or legally authorized representative must be given sufficient opportunity to consider whether or not to participate.

If a subject is unable to read or if a legally authorized representative is unable to read, an impartial witness must be present during the entire informed consent discussion. After the written informed consent and any other written information to be provided to subjects is read and explained to the subject or the subject's legally authorized representative, and after the subject or the subject's legally authorized representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and dated the informed consent form, the witness must sign and date the consent form. By signing the consent form, the witness attests to being present and observing the subject's signature. If the subject is unable to write, he/she will be required to make a mark, and at such time, there will need to be two impartial witnesses. Both will be attesting to the fact that the subject was unable to write, and placed their mark on the consent form.

No informed consent, whether oral or written, may include any exculpatory language through which the subject or legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or to release or appear to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Stratton VA Consent Template

4 REFERENCE DOCUMENTS

45 CFR 46

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 Unless waived or exempted by the IRB, the IRB may not approve a research protocol involving human subjects unless:

5.1.1 The investigator or authorized representative informs prospective subjects about all aspects of the trial and obtains the legally effective informed consent of the subject or the subject's legally authorized representative.

5.1.1.1 If someone other than the investigator conducts the interview and obtains consent from a subject, the

investigator has to formally delegate this responsibility to a person who has received the appropriate training to perform this activity.

5.1.2 The investigator or authorized representative seeks such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

5.13 The investigator or authorized representative shall communicate with prospective subjects, on an individual basis, to obtain and document informed consent. The information given to the subject or the representative is in language understandable to the subject or the representative and the impartial witness, where applicable.

5.14 The informed consent, whether oral or written, does not include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

5.15 The Stratton VA Consent Template, VA Form 10-1086, must be used as the consent form, and all required elements must be completed.

5.2 **Basic elements of Informed Consent:** Unless exempted, waived, or altered by the IRB, the IRB may not approve a research protocol involving human subjects unless in seeking informed consent the following information will be provided to each subject:

5.2.1 The name of the study and the name of the Principal Investigator conducting the study.

5.2.2 A statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.

5.2.3 A description of any reasonably foreseeable risks or discomforts to the subject.

5.2.4 A description of any benefits to the subject or to others that may reasonably be expected from the research.

5.2.5 Disclosures of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.

5.2.6 A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

5.2.7 A statement that the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), the National Institutes of Health (NIH), and the VA Office of Research Oversight (ORO) may have access to the records.

5.2.8 For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

5.2.9 An explanation of whom to contact for answers to pertinent questions about the research and research subjects rights, and whom to contact in the event of a research-related injury to the subject.

5.2.10 A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

5.2.11 A statement that if the subject takes part in the study, the subject may still have to pay the usual VA charges.

5.3 **Additional Elements of Informed Consent**: When appropriate, one or more of the following elements of information will also be provided to each subject:

5.3.1 A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant), which are currently unforeseeable.

5.3.2 Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

5.3.3 Any additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veteran's eligibility for medical care and treatment.

5.3.4 The consequences of a subject's decision to withdraw from the research and procedures for orderly Closure of participation by the subject.

5.3.5 A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.

5.3.6 The approximate number of subjects involved in the study.

5.3.7 A statement that the human biologic specimens obtained could be part of, or lead to the development of a commercially valuable product, if applicable.

5.3.8 A statement that indicates if the specimens are to be retained after the end of the study.

5.3.9 The probability for random assignment to each treatment.

5.3.10 The subject's responsibilities.

5.3.11 Information regarding payment to subjects, including the methods, amounts, schedule of payment to trial subjects, and the way payment will be prorated.

5.3.12 A statement that the monitor(s), the auditor(s), the IRB, and the regulatory authority (ies) will be granted direct access to the subject's original medical records, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally authorized representative is authorizing such access.

5.3.13 A statement that records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the research are published, the subject's identity will remain confidential.

5.4 The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth above, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

5.4.1 The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

5.4.1.1 Public benefit or service programs;

5.4.1.2 Procedures for obtaining benefits or services under those programs;

5.4.1.3 Possible changes in or alternatives to those programs or procedures; or

5.4.1.4 Possible changes in methods or levels of payment for benefits or services under those programs; and

5.4.2 The research could not practicably be carried out without the waiver or alteration.

5.5 The IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirement to obtain informed consent provided the IRB finds and documents that:

5.5.1 The research involves no more than minimal risk to the subjects;

5.5.2 The waiver or alteration will not adversely affect the rights (including privacy rights) and welfare of the subjects;

5.5.3 The research could not practicably be carried out without the waiver or alteration; and

5.5.4 Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

5.6 The IRB may require that information, in addition to that specifically mentioned above, be given to the subjects when in the IRB's judgment the information would add to the protection of the rights and welfare of subjects.

5.7 The informed consent requirements in this SOP are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

5.8 The IRB will not review or approve research that requests a waiver of the requirements for informed consent per 21 CFR 50.24 "Exception from informed consent requirements for emergency research."

5.9 Documentation of Informed Consent

5.9.1 Informed consent must be documented by the use of a written form approved by the IRB, and signed and dated by:

5.9.1.1 The subject or the subject's legally authorized representative,

5.9.1.2 An impartial witness whose role is to witness the subject's or the subject's legally authorized representative's signature, and

5.9.1.3 The person obtaining the informed consent.

5.9.2 VA Form 10-1086 must be used as the consent form.

5.9.2.1 A note must be placed under the witness' signature line if the sponsor or the IRB requires a witness to the consent process in addition to the witness to the subject's signature or

5.9.2.2 If the same person needs to serve both capacities. Should this become necessary, then it should be documented in the subject's medical record and in the IRB file.

5.9.2.3 The consent form must be the most recent IRB approved consent form and must include the stamped approval and expiration dates on each page.

5.9.2.3.1 The IRB must maintain a copy of each approved consent form in its records.

5.9.2.4 The original signed consent form must be filed in the subject's case history.

5.9.2.5 A copy of the signed informed consent must be provided to the subject or the subject's legally authorized representative.

5.9.3 The subject's involvement in research must be documented in the individual's electronic medical record to protect the subject's safety.

5.9.3.1 The required information in the medical record includes:

5.9.3.1.1 The title of the research study.

5.9.3.1.2 The name of the Principal Investigator and other relevant study personnel.

5.9.3.1.3 The name of the individual who obtains the informed consent.

5.9.3.1.4 Contact information in case of emergency or need for further information regarding the study or therapy.

5.9.3.1.5 A statement that the study was explained to the subject.

5.9.3.1.6 A statement that the subject was given the opportunity to ask questions.

5.9.3.1.7 Study inclusion and exclusion criteria and documentation that the subject met all of the criteria.

5.9.3.1.8 A note indicating when the subject actually entered into the study and when the subject's participation in the study is terminated.

5.9.3.1.9 All other information appropriate to the study.

5.9.3.2 The IRB does not flag the medical record if:

5.9.3.2.1 The subject's participation in the study involves only one encounter, only the use of a questionnaire, or the use of previously collected biological specimens.

5.9.3.2.2 The identification of the patient as a subject in a particular study would place the subject at greater than minimal risk.

5.9.4 A short form of the written consent document stating the elements of informed consent and presented orally to the subject or the subject's legally authorized representative may be used if:

5.9.4.1 The IRB approves the written summary of what is to be said to the subject or the subject's legally authorized representative.

5.9.4.2 Only the short form is to be signed by the subject or the subject's legally authorized representative.

5.9.4.3 The witness must sign both the short form and a copy of the summary, and the person actually obtaining the consent must sign a copy of the summary.

5.9.4.4 The original short form and summary must be filed in the subject's case history.

5.9.4.5 A copy of the summary must be given to the subject or the subject's legally authorized representative, in addition to a copy of the signed short form.

5.10 Waiver of Documentation of Informed Consent

5.10.1 The IRB may waive the requirement for the investigator to obtain a signed informed consent form for some or all subjects, if it finds either:

5.10.1.1 That the only record linking the subject and the research is the consent and the principal risk to the subject would be potential harm resulting from a breach of confidentiality.

5.10.1.1.1 Each subject must be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or

5.10.1.2 That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

5.10.2 When the documentation requirement is waived, the IRB must document the reason for the waiver and may require the investigator to provide subjects with a written statement regarding the research.

5.11 An addendum consent may be required if:

5.11.1 The investigator or the IRB determines that additional information regarding the study should be distributed to subjects.

5.11.1.1 The addendum consent format should include the basic elements of consent as in 5.2.

5.11.1.2 The investigator may revise the original approved consent form, in lieu of an addendum consent, to be reviewed and approved by the IRB.

5.12 Informed consent copies are to be sent to the Research Office within 5 days of obtaining signature, and to HIMS for scanning into EMR.

5.13 The IRB does not permit the use of a group consent process.

TITLE	**Mandatory Training for Investigators**	
Document number	**IRB-011**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 02/26/2004**

INR 6A&B

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required for assuring that all investigators are knowledgeable about the ethical principles and regulatory requirements associated with research involving human subjects at Stratton VA Medical Center.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Human Research Protection Program Training Policy

Station Memorandum SL-151-04: Human Studies Subcommittee

The Declaration of Helsinki

The Belmont Report

38 CFR 16, 17

45 CFR 46

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

4 REFERENCE DOCUMENTS

N/A

5 PROCEDURE

5.1 Principal Investigators and their research staff must complete the initial training program, and comply with continuing education requirements every calendar year, as outlined in the Human Research Protection Program Training Policy.

5.2 Investigators will not be allowed to initiate their research until all educational requirements are met with appropriate documentation provided to the Research Office, and Final IRB and R&D approval have been received.

5.3 Initial training

5.3.1 The participant is provided the following items to read for initial training:

5.3.1.1 Human Research Protection Program Training Policy

5.3.1.2 Station Memorandum SL-151-04: Human Studies Subcommittee

5.3.1.3 Institutional Review Board Standard Operating Procedures

5.3.1.4 The Declaration of Helsinki

5.3.1.5 The Belmont Report

5.3.1.6 38 CFR 16

5.3.1.7 45 CFR 46

5.3.2 The participant must complete and successfully pass the Initial Human Studies training test.

5.3.2.1 A score of 80% is considered passing or the test must be retaken.

5.3.2.2 2 hours of educational credit will be issued upon successful completion of the test.

5.3.3 The participant must complete and successfully pass the Health Insurance Portability and Accountability Act (HIPAA) training test.

5.3.3.1 A score of 80% is considered passing or the test must be retaken.

5.3.3.2 1 hour of educational credit will be issued upon successful completion of the test.

5.3.4 The participant must submit a certificate to the Research Office indicating the successful completion of Good Clinical Practice training (http://vaww.ees.aac.va.gov for VA employees or https://www.ees-learning.net for non-VA employees).

5.4 All participants who will potentially obtain signed informed consent from research subjects are required to complete and successfully pass the Informed Consent training test.

5.4.1 A score of 80% is considered passing or the test must be retaken.

5.4.2 2 hours of educational credit will be issued upon successful completion of the test.

5.5 Continuing Education

5.5.1 It is required that Principal Investigator(s) and their research staff directly involved with a human studies protocol submit a certificate to the Research Office indicating the successful completion of the annual GCP training provided by Central Office (http://vaww.ees.aac.va.gov for VA employees or https://www.ees-learning.net for non-VA employees)
Educational credit will be issued upon successful completion of the requirement.

5.5.1.1 Continuation approval will not be granted unless the continuing educational requirement is met.

5.6 If the subject receives less than 80% on an examination, the subject is offered the opportunity to review the incorrect answers. The subject is required to take another examination offered by the Research Office and obtain a passing grade of 80%.

5.7 If the subject receives less than 80% on the second examination, a remedial action plan is put in place.

5.7.1 The HRPP Coordinator assesses the subject's knowledge of the questions missed on the examinations and presents the information to the IRB Chair or designee and/or the ACOS R&D.

5.7.2 Additional related reading materials may be assigned to the subject by the IRB Chair or designee.

5.7.3 Once the subject completes any additional requirements, the subject may be asked to complete another examination.

5.8 Educational training records are maintained in the Research Office in the database.

5.9 The Research Office reviews the investigator training program annually.

5.10 Changes to the Mandatory Training Program may be implemented at the discretion of the ACOS R&D.

5.11 The Human Research Protection Program Training Policy outlines the educational training requirements for non-VA investigators, students, and VISN research.

5.12 The IRB may require additional training for anyone involved in human subject research, as needed for remediation, for specific reasons, or for changes in VHA or other agency requirements. Noncompliance with educational requirements will result in placement on the ineligible list, and suspension of ability to perform human subject research.

TITLE	**Membership and Management**	
Document number	**IRB-012**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 03/04/2004**

INR 2C, 3A

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to detail the membership and management of the IRB for review of research.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

IRB Experienced Member memo

4 REFERENCE DOCUMENTS

45 CFR 46

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 All CV's of potential IRB Chairs, Vice-Chairs, or members are reviewed by the ACOS R&D to ascertain the background and qualifications of the potential member.

5.2 The Medical Center Director appoints the Chair and Vice-Chair of the IRB in writing.

5.2.1 The appointments are for one year and may be re-appointed indefinitely in writing.

5.3 The Medical Center Director appoints IRB members in writing.

5.3.1 Recommendations for IRB membership are made by IRB members and R&D Committee members according to the needs

of the IRB. Members are selected based on background, qualifications, and the diverse needs of the IRB. Potential conflicts of interest are taken into consideration in the selection of new members.

5.3.2 Other VA personnel may submit names to the IRB or R&D Committee to be forwarded to the Medical Center Director for consideration.

5.3.3 Members of the VA IRB must be appointed by the Medical Center Director for a period of 3 years, and may be re-appointed indefinitely. Members may resign from the IRB at any time.

5.3.4 VA representatives to affiliate IRBs must be appointed by the Medical Center Director for a period of 3 years, and may be re-appointed indefinitely. Members may resign from the IRB at any time.

5.3.4.1 Two or more VA employees must serve as voting members of the affiliate IRB that reviews VA research.

5.3.4.2 At least one of these members must have scientific expertise.

5.3.4.3 VA members must serve as full members of the IRB, which includes the review of non-VA research.

5.3.4.4 At least one of these members must be present during the review of VA research.

5.3.5 IRB members are voting or non-voting members.

5.3.5.1 The ACOS R&D, AO for R&D, and the Research Compliance Officer serve as ex-officio non-voting members of the IRB. R&D administration officials may not serve as voting members of the IRB.

5.3.5.2 All other members are voting members.

5.4 The Medical Center Director appoints IRB members to ensure that:

5.4.1 The IRB has at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

5.4.2 The members of the IRB are qualified through expertise and diversity, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, and promote respect for the IRB's advice and counsel in safeguarding the rights and welfare of human subjects.

5.4.3 The IRB includes persons with the professional competence necessary to review research activities regularly reviewed by the IRB.

5.4.4 The IRB includes persons knowledgeable of institutional commitments and regulations, applicable law, and standards of professional conduct and practice so as to be able to ascertain the acceptability of proposed research in terms of these issues.

5.4.5 The IRB includes one or more individuals who are knowledgeable about and experienced in working with categories of vulnerable subjects involved in research regularly reviewed by the IRB. Vulnerable categories of subjects may include children, prisoners, pregnant women, or handicapped or mentally disabled persons.

5.4.6 In a non-discriminatory manner, the IRB does not consist entirely of men or entirely of women, or consist entirely of individuals from one profession. No member will be selected to serve on the IRB merely on the basis of gender.

5.4.5 The IRB includes at least one member whose primary expertise is in scientific areas, and one member whose primary expertise is in non-scientific areas.

5.4.6 The IRB includes at least one member who is not affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

5.4.7 The IRB cannot have a member participate in the review of research in which the member has a Conflict of Interest, except to provide information requested by the IRB.

5.5 The IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond, or in addition to that available on the IRB.

5.5.1 Consultants are not considered IRB members and do not vote.

5.5.2 Any IRB member may request a consultant by making a verbal or written request to the IRB Chair or designee.

5.5.3 The IRB Chair or designee will review the qualifications of the consultant prior to the consultant’s participation in the review of the research.

5.6 IRB members review proposed research at convened meetings at which a majority of the voting members of the IRB are present, including at least one voting member whose primary expertise is in nonscientific areas.

5.6.1 In order for research to be approved, it must receive the approval of a majority of those voting members present at the meeting.

5.6.2 Conference calls or video-conference procedures may be used at a convened meeting, if a member has received copies of the documents that are to be reviewed at the meeting. The member may vote and be considered as part of the quorum.

5.6.3 IRB members may not participate in the review of any research in which the member has a conflict of interest, except to provide information requested by the IRB. The research will not be voted upon should quorum be lost due to the absence of the member(s) with a conflict of interest.

5.6.4 IRB members with a conflict of interest in the research are expected to declare the reasons for the conflict to the IRB prior to the review of research.

5.6.5 The IRB may consider the comments of members who cannot attend the convened meeting. Absent members are not considered in the quorum or voting of IRB meetings.

5.7 The Stratton VA may use alternate members for the IRB.

5.7.1 The Medical Center Director appoints alternate IRB members in writing.

5.7.1.1 The term of appointment is the same as the term of the primary member.

5.7.2 The IRB roster will identify the primary IRB member for whom the alternate member may substitute.

5.7.3 The alternate member's qualifications must be comparable to those of the primary member to be replaced.

5.7.4 When an alternate member replaces the primary member at a convened meeting, the primary member must assure the alternate member receives and reviews the meeting materials in advance of the meeting.

5.7.4.1 The alternate member has the same privileges as the primary member, i.e. reviews and votes on protocols at a convened IRB meeting.

5.7.5 The alternate member should receive the same IRB training as primary members.

5.7.6 The alternate should attend as many IRB meetings as possible, even when not required to be present as a formal alternate.

5.7.7 The alternate member is allowed to replace the primary member 3 times per year.

5.7.8 The IRB meeting may not be conducted if alternates constitute the majority of the members present.

5.7.9 The IRB minutes must document when an alternate member replaces a primary member.

5.8 All IRB members are required to attend at least 6 out of 12 IRB meetings per calendar year, with the exception of those members covered under a Memorandum of Understanding (MOU).

5.9 In the absence of the Chair, the Vice-Chair or designee is the acting Chair.

5.10 The Stratton VA liability Federal Tort Claims Act (FTCA) covers authorized actions of IRB members taken in their official capacity as IRB members.

5.11 The IRB staff maintains a file of the current curricula vitae of IRB members.

5.12 Any change in IRB membership is reported to Office of Human Research Protections (OHRP) and the Office of Research Oversight (ORO) by the Research Office.

5.13 The Medical Center Director, at his or her discretion, may remove IRB members, the Chair or Vice-Chair for cause only after an administrative investigation or other disciplinary action is completed.

5.14 A list of scheduled IRB meetings and the membership roster is available on the P drive (IRB folder) and on the VISN 2 Research website.

TITLE	**Review of Advertising**	
Document number	**IRB-013**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 03/04/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required for the review of advertising when used to recruit human subjects for participation in research.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Expedited Review Revision/Amendment Approval letter

Protocol Review Request Form for Revision/Amendment

Full Committee Review Revision/Amendment Approval letter

4 REFERENCES

45 CFR 46

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 Advertising is considered by the IRB to be part of the informed consent process. Advertising should be included as part of the initial research submission. Advertising not included as part of the initial submission is a revision to the research and must be submitted for review. (Refer to IRB-006 Revisions to Previously Approved Research)

5.1.1 The final copy of the advertisement should be submitted except when a videotape or audiotape will be used.

5.1.2 A written script should be submitted for video or audio advertising before production of the final version to allow for any revisions/changes to the wording that the IRB may require. The final version must be submitted later for review.

5.2 The IRB reviews advertising to assure:

5.2.1 The advertising is not unduly coercive and does not unduly influence subjects by implying benefit, especially those subjects who are likely to be vulnerable.

5.2.2 The advertising does not promise a certainty of benefit beyond that outlined in the research protocol and informed consent.

5.2.3 The advertising makes no implicit or explicit claim that the drug, biologic, device, or research procedure is safe, effective, or is equal or superior to available treatments.

5.2.3.1 Words such as “new treatment”, “new medication”, or “new drug” are not used without an explanation of the investigational aspects of the research.

5.2.3.2 FDA regulated investigational products must be identified as investigational or experimental.

5.2.4 The advertisement does not emphasize payment or amount of payment.

5.2.5 The advertisement does not promise free medical treatment when the intent is only to say that subjects will not be charged for procedures required by the investigation.

5.3 The IRB recommends that advertisements be limited to the information necessary for potential subjects to determine their eligibility and interest. The advertisement may contain the following information:

5.3.1 The name and address of the Principal Investigator and/or the name of the research facility.

5.3.2 The condition under study and/or the purpose of the research.

5.3.3 A summary of criteria used to determine eligibility for the study.

5.3.4 A brief list of the potential benefits of participation, if any.

5.3.5 The approximate time commitment or other commitments of potential subjects.

5.3.6 The location of the research and/or whom to contact for further information.

5.4 Any press release related to the research must first be submitted to the Stratton VA Public Relations office for approval. The advertising, with the approval letter from the Public Relations Office, should be submitted to the Research Office for review and approval by the IRB.

5.5 Expedited Review Process:

5.5.1 A member of the IRB staff pre-reviews the advertisement. The IRB Chair or designee conducts the review of the advertisement and may not have a conflict of interest with the research.

5.5.2 The IRB Chair or designee conducting expedited review has the final authority in deciding whether the advertisement qualifies for expedited review and may recommend full committee review.

5.5.3 In order to approve advertisements by expedited review, the reviewer shall determine that criteria for approval of research (38 CFR 16.111) are satisfied.

5.5.4 If the reviewer requests changes or additional information, the IRB staff contacts the Principal Investigator or the designated contact person and requests the information. Upon receipt of the requested information, the changes or additional information is forwarded to the reviewer.

5.5.5 If the reviewer still cannot approve the advertisement as submitted, the Principal Investigator or designated contact person is notified. The Principal Investigator may modify the advertisement for resubmission to the IRB or resubmit the advertisement for review at a full IRB meeting.

5.5.6 If the reviewer recommends full committee review, the Principal Investigator or designated contact person is notified that the advertisement must be reviewed by the full committee and is asked to provide additional copies of the research submission.

5.5.7 The reviewer may not disapprove advertisements under Expedited Review.

5.5.8 If the reviewer finds the advertisement acceptable,

5.5.8.1 The IRB Chair or designee who reviewed the advertisement approves the advertisement.

5.5.8.2 The IRB Chair or designee signs and dates the Expedited Review Revision/Amendment Approval letter.

5.5.8.3 The Expedited Review Revision/Amendment Approval letter is sent to the Principal Investigator. A brief description of the advertisement is included in a parenthetical after the protocol title in the approval letter.

5.5.8.4 The IRB is notified of the approval with a short description of the advertisement in the agenda and in the minutes of the next scheduled IRB meeting.

5.6 Full Committee Review Process:

5.6.1 Advertisements that require full committee review are placed on the agenda of the monthly IRB meeting and are distributed approximately two weeks in advance of the meeting. The advertisement is summarized on the agenda and the agenda identifies all IRB members who are also participating in the research to alert the committee to a conflict of interest.

5.6.2 The IRB staff assigns two primary reviewers, who are not participating in the research, based on their area of expertise.

5.6.3 Committee members are given a copy of the advertisement and the Protocol Review Request Form (Revision/Amendment) to review.

5.6.4 Primary reviewers are given a copy of the advertisement, Protocol Review Request Form (Revision/Amendment), and the primary reviewer sheet to record their comments.

5.6.5 The IRB staff takes minutes at the IRB meeting pertaining to discussion of the advertisement.

5.6.6 Minutes are prepared within one week after the meeting and include:

5.6.6.1 Attendance of IRB members at the meeting.

5.6.6.2 The votes for, against, abstaining, recused, and excused. IRB members with a conflicting interest must recuse themselves from voting.

5.6.6.3 Modifications or any other changes to the advertisement required by the IRB.

5.6.6.4 The basis for requiring changes in or disapproving research.

5.6.6.5 A written summary of any discussion of controverted issues and their resolution.

5.6.7 If the advertisement is approved as submitted,

5.6.7.1 A Full Committee Review Revision/Amendment Approval letter indicating that the advertisement was approved as submitted is sent to the Principal Investigator(s).

5.6.7.2 The Date of Approval for research approved by the full IRB is the date of the IRB meeting at which the advertisement was approved.

5.6.8 If the research is approved with modifications,

5.6.8.1 The modifications must be documented in sufficient detail to allow the IRB staff to verify the changes required by the IRB.

5.6.8.2 A Notification of Approval with Contingencies, listing all required modifications and conditions for approval, is sent to the Principal Investigator(s).

5.6.8.3 The Principal Investigator(s) responds to the Research Office with a copy of all modified documents.

5.6.8.4 The IRB staff reviews the modified documents for confirmation of all modifications required by the IRB.

5.6.8.5 If the submitted documents have not been modified as required, the Principal Investigator(s) is contacted by the IRB staff and asked to submit the complete revision as requested.

5.6.8.6 Once the IRB staff determines that the documents contain all required modifications,

5.6.8.6.1 The IRB Chair or designee reviews the revised documents by Expedited Review and signs the Full Committee Review Revision/Amendment approval letter as per the instructions of the IRB at the full committee meeting at which the revision was reviewed or,

5.6.8.6.2 The modified documents are distributed to all committee members and the original primary reviewers for review and approval at the next full IRB meeting.

5.6.8.7 If the Principal Investigator(s) does not return the required modified documents within 30 days from the date the letter was issued, the IRB staff will notify the IRB Chair or designee to determine a course of action.

5.6.8.8 The Date of Approval is the date of the meeting at which the research was approved with modifications.

5.6.9 If the advertisement is disapproved, the IRB Chair or designee notifies the Principal Investigator in writing of the reasons for the disapproval and offers the Principal Investigator an opportunity to resubmit the revision to the IRB.

5.7 The advertisement and copies of documents received and sent are filed in the Research Office.

TITLE	**Training for IRB Members**	
Document number	**IRB-014**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 02/12/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to detail the training IRB members receive.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

Human Research Protection Program Training Policy
Station Memorandum SL-151-04: Human Studies Subcommittee
IRB Member Policy
Institutional Review Board Standard Operating Procedures
The Declaration of Helsinki
The Belmont Report
The Nuremberg Code
38 CFR 16, 17
45 CFR 46
IRB Member Handbook
IRB Member Policy

4 REFERENCE DOCUMENTS

N/A

5 PROCEDURE

5.1 New appointed IRB Members

5.1.1 The IRB Staff contacts the new IRB member and encourages them to schedule an orientation meeting with the staff prior to attending their first IRB meeting.

5.1.1.1 The orientation will cover the following topics:

5.1.1.1.1 IRB member policy (education & attendance)

5.1.1.1.2 Research Office contact information

5.1.1.1.3 IRB member roster

5.1.1.1.4 Use of primary reviewer form

5.1.1.1.5 Outline of agenda/minutes packet, MIRB database

5.1.2 The new IRB member is also encouraged to schedule an appointment with the IRB Chair or designee to review responsibilities as an IRB member.

5.1.3 The new IRB member receives a copy of the following materials:

5.1.3.1 Human Research Protection Program Training Policy

5.1.3.2 Station Memorandum SL-151-04: Human Studies Subcommittee

5.1.3.3 IRB Member Policy

5.1.3.4 Institutional Review Board Standard Operating Procedures

5.1.3.5 The Declaration of Helsinki

5.1.3.6 The Belmont Report

5.1.3.7 38 CFR 16, 17

5.1.3.8 45 CFR 46

5.1.3.9 IRB Member Policy

5.1.3.10 IRB Member Handbook

5.2 All IRB members

5.2.1 Initial Training to be completed within first 6 months of membership:

5.2.1.1 VA Human Studies training packet and written test. Two hours of educational credit will be issued upon successful completion of the test. A score of 80% is considered passing or the test must be retaken.

5.2.1.2 Health Insurance Portability and Accountability Act (HIPAA) training packet and written test. 1 hour of educational credit will be issued upon successful completion of the test. A score of 80% is considered passing or the test must be retaken.

5.2.1.3 Good Clinical Practice (GCP) training for current calendar year – completed online at http://vaww.ees.aac.va.gov for VA employees https://www.ees-learning.net for non-VA employees. Educational credit will be issued upon successful completion of the requirement.

5.2.1.4 Informed Consent training packet and written test. 2 hours of educational credit will be issued upon successful completion of the test. A score of 80% is considered passing or the test must be retaken.

5.2.2 Continuing Education

5.2.2.1 The IRB Chair or designee will present at least 6 educational topics annually at the Institutional Review Board meeting.

5.2.2.2 Members will receive a copy of the bi-monthly publication "IRB Ethics & Human Research".

5.2.2.3 Good Clinical Practice (GCP) annual training for current calendar year – completed online at http://vaww.ees.aac.va.gov for VA employees https://www.ees-learning.net for non-VA employees. Educational credit will be issued upon successful completion of the requirement.

5.2.2.4 IRB meeting minutes are prepared that include:

5.2.2.4.1 Attendance of IRB members at the education session and the IRB meeting.

5.2.2.4.2 Educational information presented to the Committee at the meeting.

5.2.2.4.3 Educational information sent to the Committee before the meeting.

5.2.3 Standard Operating Procedures (SOPs)

5.2.3.1 All IRB members are requested to review the IRB SOPs.

5.2.3.1.1 Copies of the SOPs are available for review in the Research Office, A-603, during normal business hours.

5.2.3.1.2 The SOPs are also available on the P drive and on the VISN 2 Research website.

TITLE	**Processing of Deviations**	
Document number	**IRB-015**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 05/17/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state and local regulations, and ICH guidelines in the conduct of clinical research studies. Written procedures are required for processing reports of deviations.

The IRB's policy requires the Principal Investigator to report to the IRB upon discovery, any "Significant Deviation" to the IRB-approved protocol that may potentially affect the rights, safety, and welfare of the subjects, such as:

a. Administrative or procedural infractions in the implementation of the protocol or informed consent.
b. Significant changes to the IRB-approved protocol that may potentially affect the rights, safety, and welfare of the subjects.

All changes in previously approved protocols must be promptly reported to the IRB. The proposed changes must not be initiated without review and approval except where necessary to eliminate apparent immediate hazards to subjects.

The Principal Investigator(s) may contact the IRB Chair or designee with questions regarding whether or not a potential deviation poses a risk to subjects. The IRB will make the final determination as to the level of risk.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

IRB-003 "Suspension and Closure of Approved Research by the IRB"

4 REFERENCE DOCUMENTS

45 CFR

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

5.1 "Significant Deviations": Any departure from the procedures stated in the approved research protocol or informed consent that increases the risk to

subjects. The deviation is required to be reported to the IRB within 5 days of the incident. Examples include but are not limited to the following:
a. Infractions involving dosing/distribution of study medications causing risk to the subject
b. Infractions in following the guidelines for proper informed consent execution (i.e. using an expired informed consent)
c. Infractions in which the sponsor (if applicable) requests notification to the IRB
d. Infractions in which research procedures performed outside the approved research protocol increased risk to subjects

Principal Investigators must report "Significant Deviations" to the IRB upon discovery, and no later than 5 days, by submitting a letter that will include, but is not limited to, the following: a description of the deviation, an explanation of why the deviation occurred, a corrective action plan, and an explanation of what is being done to prevent a future occurrence. If the study is a sponsored study, the letter should indicate if the sponsor was notified of the deviation.

5.2 Upon receipt of the deviation letter, the IRB staff stamps it with a date of receipt. The information is reviewed for completeness and accuracy by the IRB staff and is entered into the database.

5.2.1 If any items are missing or there are questions about the deviation, the Principal Investigator or the designated contact person may be contacted by the IRB staff and requested to provide additional information or documents.

5.3 The IRB Chair or designee, the Research Compliance officer, and the ACOS R&D will review the deviation letter to determine whether any revisions or actions are required and if so, will refer the deviation to the full IRB to review and determine the actions required. The IRB is notified of all "significant deviations" in the agenda of the next scheduled IRB meeting.

5.4 If the IRB Chair or designee or the full IRB request any modification to the consent document or research protocol, or addendum consent, the IRB Chair or designee will send a notification to the Principal Investigator to submit the modifications to the IRB for review. If the IRB does not receive the complete modification or a satisfactory explanation as to why the modification could not be completed within four weeks,

5.4.1 The Principal Investigator is sent a Notification indicating failure to comply with a request for modification. A copy will be sent to the Care Line Leader and the institutional official.

5.4.2 The research is suspended following IRB-AD-003 "Suspension and Closure of Approved Research by the IRB."

5.4.3 The Principal Investigator becomes ineligible to submit new protocols.

5.4.4 The Principal Investigator remains ineligible until a complete modification is received by the IRB and all other deficiencies are resolved.

5.4.5 The list of ineligible Principal Investigators will be distributed to IRB members with the agenda and included with the meeting minutes.

5.5 If the IRB Chair or designee or the full IRB determines that a significant deviation requires reporting, then

5.5.1 The IRB staff prepares a report of the event and corrective actions to be taken.

5.5.2 The IRB staff sends a copy of the report signed by the IRB Chair or designee to the Care Line Leader and the institutional official.

5.5.3 A copy of the report is included with the agenda for the next scheduled IRB meeting.

5.5.4 The IRB staff forwards a copy of the notification to Office for Human Research Protections (OHRP), Food and Drug Administration (FDA), Office for Research Oversight (ORO), and the sponsor, as applicable, within 10 working days of the IRB's determination.

TITLE	**IRB Review of Research**	
Document number	**IRB-016**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 04/08/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, local, and ICH guidelines in the conduct of clinical research studies. Written procedures are required to guide the IRB in the review of research.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

None

4 REFERENCES

45 CFR 46

21 CFR 50, 56

38 CFR 16

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

5 PROCEDURE

INR 6C

5.1 The IRB will review and have authority to approve, require modifications n (to secure approval), or disapprove all research activities covered by the Stratton VA Medical Center OHRP Federal Wide Assurance (FWA #00002073).

5.2 The IRB will require that information given to subjects as part of informed consent is in accordance with "Informed Consent, IRB – 010". The IRB may require that information, in addition to that specifically mentioned in "Informed Consent, IRB – 010" be given to the subjects when in the IRB's judgment the information would add to the protection of the rights and welfare of subjects.

5.3 The IRB will require documentation of informed consent or may waive documentation in accordance with "Informed Consent, IRB – 010".

5.4 The IRB will notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of

modifications required to secure IRB approval of the research activity as per "Initial Review of Research, IRB – 001", "Continuing Review of Research, IRB – 002", and "Revisions to Previously Approved Research, IRB – 006". If the IRB decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond as per "Initial Review of Research, IRB – 001", "Continuing Review of Research, IRB – 002", and "Revisions to Previously Approved Research, IRB – 006".

5.5 The IRB will conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year, and will have authority to observe or have a third party observe the consent process and the research.

5.6 The IRB will monitor changes in VA and other Federal regulations and policies that relate to Human Research Protections.

5.7 Research is considered exempt from the regulations if:

5.7.1 The research does not involve the use of an FDA regulated test article; and

5.7.2 The only involvement of human subjects will be in one or more of the following categories:

5.7.2.1 Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

5.7.2.1.1 Research on regular and special education instructional strategies, or

5.7.2.1.2 Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

5.7.2.2 Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:

5.7.2.2.1 Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects, and any disclosure of the human subjects' responses outside the research would reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

5.7.2.3 Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under the previous section, if:

5.7.2.3.1 The human subjects are elected or appointed public officials or candidates for public office; or

5.7.2.3.2 Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

5.7.2.4 Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

5.7.2.5 Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:

5.7.2.5.1 Public benefit or service programs;

5.7.2.5.2 Procedures for obtaining benefits or services under those programs;

5.7.2.5.3 Possible changes in or alternatives to those programs or procedures; or

5.7.2.5.4 Possible changes in methods or levels of payment for benefits or services under those programs.

5.7.2.6 Taste and food quality evaluation and consumer acceptance studies:

5.7.2.6.1 If wholesome foods without additives are consumed; or

5.7.2.6.2 If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural, chemical, or environmental contaminant at or below the level found to be safe, by the

Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

5.8 An IRB may use the Expedited Review procedure to review either or both of the following:

5.8.1 Some or all of the research published in the Federal Register, 63 FR 60364-60367 "Protection of Human Subjects: Categories of Research That May be Reviewed by the Institutional Review Board (IRB) Through an Expedited" (dated November 9, 1998), and found by the IRB Chair or designee to involve no more than minimal risk and/or

5.8.2 Minor changes in previously approved research during the period (of 365 days or less) for which approval is authorized.

5.9 In order to approve research the IRB will determine that the research is exempt from the regulations or that all of the following requirements are satisfied:

5.9.1 Risks to subjects are minimized:

5.9.1.1 By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

5.9.1.2 Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

5.9.2 Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably be expected to result.

5.9.2.1 In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research.)

5.9.2.2 The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

5.9.3 Selection of subjects is equitable. In making this assessment the IRB should take into account the purpose of the research and the setting in which the research will be conducted, and should

consider the scientific and ethical reasons for including vulnerable subjects in the research.

5.9.4 Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by, "Informed Consent, IRB – 010."

5.9.5 Informed consent will be appropriately documented, in accordance with, and to the extent required by, "Informed Consent, IRB – 010."

5.9.6 When appropriate, the research plan will make adequate provisions for monitoring the data collected to ensure the safety of subjects.

5.9.7 When appropriate, there will be adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

5.9.8 When some or all of the subjects are likely to be vulnerable to coercion or undue influence, the research includes additional safeguards to protect the rights and welfare of these subjects.

5.9.8.1 If the research involves adults who do not have the capacity to consent for themselves, the IRB will also follow "Research Involving Adults who Lack Capacity to Provide Informed Consent, IRB – 005."

5.9.9 The amount and method of payment to subjects neither presents problems of coercion or undue influence on the trial subjects. When appropriate, payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

5.10 **Research Involving Investigational Devices:** The Stratton VA Medical Center does not conduct research involving investigational devices.

5.10.1 At the time an investigator indicates he/she would like to conduct research on an investigational device, the SOPs will be updated to include the appropriate procedures.

5.10.2 The Stratton VA Medical Center Pharmacy must have procedures in place for receipt, storage, security, dispensing and disposition of unused stock.

5.11 Nothing in this SOP is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

Standard Operating Procedures For Human Studies Research

Department of Veteran Affairs, Albany, New York

Addendum to "IRB Review of Research, IRB-016"
Effective Date: September 22, 2005

DEFINITIONS

Signficant risk device: an investigational device that presents a potential for serious risk to the health, safety or welfare of a participant and (a) is intended as an implant; (b) is purported or represented to be for use in supporting or sustaining human life; (c) is for a use of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or (d) otherwise presents a potential for serious risk to the health, safety or welfare of a subject.

Non-significant risk device: a device that does not meet the definition for a significant risk study

REFERENCES

21 CFR 812

Research Involving Investigational FDA Regulated Test Articles. Medical products, such as drugs, biologics, and medical devices need to be proven safe and effective before the FDA can approve them for sale to and use by patients. FDA reviews the results of laboratory, animal and human clinical testing to determine if the product to be put on the market is safe and effective. New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy.

(1) An approved investigational device exemption (IDE) permits a device not approved by FDA to be shipped to conduct clinical investigations of that device. Not all investigational devices need an IDE.

(2) With only a few exceptions, most clinical research being done on FDA regulated test articles with either an IND or IDE will need initial review at a convened IRB meeting.

No claims should be made, either explicitly or implicitly, that the drug, biologic, or device is safe or effective for the purposes under investigation, or that the test article is known to be equivalent or superior to any other drug, biologic, or device.

Investigator and Sponsor Responsibilities. The interrelationship and interaction between the research sponsor (e.g., drug and device manufacturer) the clinical investigator and the IRB may be very complex. Sponsor-IRB interaction customarily occurs through the investigator who conducts the clinical study. The clinical investigator generally provides the communication link between the IRB and the sponsor. Such linkages are agreed to by the sponsors and the investigator when they sign forms FDA 1571 and FDA 1572. There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The clinical investigator should be kept apprised of the discussion. Because clinical investigators work directly with the IRB, it is appropriate that they assure the sponsor that the IRB is functioning in compliance with the regulations. The IRB must notify an investigator in writing of its decision to approve, disapprove or request modifications in a proposed research activity [21 CFR 56.109(e)]. This correspondence should be made available to the sponsor by the clinical investigator.

Under FDA regulations, the investigator in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. These responsibilities include:

(1) Obtaining IRB approval;

(2) Obtaining informed consent from each participant;

(3) Following the investigational plan;

(4) Complying fully with the regulations;

(5) Protecting the rights, welfare and safety of the participants;

(6) Supervising the use and disposition of the test article;

(7) Maintaining accurate, current and complete records; and

(8) Disclosing relevant financial information.

The investigator also makes a commitment subject to an institutional board review requirement (under Part 56) to:

(1) be responsible for the initial and continuing review and approval of the clinical investigation;

(2) promptly report to the IRB all changes in the research activity;

(3) promptly report all unanticipated problems involving risks to human participants or others, and

(4) not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to the human participants.

The sponsor takes responsibility for initiating the clinical investigation and holding the IND or IDE in most cases, but does not usually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals or medical center can also be considered a sponsor for an investigation. An investigator is referred to as the sponsor-investigator when the individual investigator is also the initiator of the clinical investigation. Some of the responsibilities of sponsors are:

(1) Selecting qualified investigators;

(2) Providing investigators with the information they need to conduct the investigation properly;

(3) Ensuring proper monitoring of the investigation; and

(4) Ensuring that the FDA and (for devices) any reviewing IRB or (for drugs) all participating investigators are promptly informed of significant new information about an investigation.

IRB Review of Investigational Medical Devices. Investigational devices can only be used after appropriate review and approval of the protocol submission and supporting documents.

Investigators initiating or participating in research under an IDE must adhere to FDA, OHRP, and VA regulations. The Principal Investigator is responsible for the storage, security and dispensing of the device as outlined in the approved research protocol. The PI maintains records and tracking of investigational devices. All investigational medical devices must be stored in a secure location, accessible only to study personnel. The storage area must meet any conditions provided by the manufacturer related to environmental review. Investigational medical devices will be dispersed only to participants in the approved research protocol who have signed an informed consent form and HIPAA authorization.

Clinical investigations of medical devices must comply with the FDA informed consent and IRB regulations [21 CFR 50 and 56, respectively]. FDA device regulations differentiate between significant risk (SR) and non-significant risk

(NSR) devices. A significant risk device must have an IDE, while a non-significant risk device does not. Thus, if a clinical investigation is submitted to the IRB for a device that has an IDE, the device is considered a SR device.

For both SR and NSR device studies, IRB approval prior to conducting clinical trials and continuing review by the IRB are required. In addition, informed consent must be obtained for either type of study [21 CFR 50].
The risk determination should be based on the proposed use of a device in an investigation, and not on the device alone. In deciding if a study poses a SR, the IRB must consider the nature of the harm that may result from use of the device. Studies where the potential harm to participants could be life threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to body structure should be considered SR. Also, if the participant must undergo a procedure as part of the investigational study, e.g., a surgical procedure, the IRB must consider the potential harm that could be caused by the procedure in addition to the potential harm caused by the device.

FDA has the ultimate decision in determining if a device study is SR or NSR. If the FDA does not agree with the IRB's decision that a device study presents a NSR, an IDE application must be submitted to FDA. On the other hand, if a sponsor files an IDE with FDA because it is presumed to be an SR study, but FDA classifies the device study as NSR, the FDA will return the IDE application to the sponsor and the study would be presented to IRB as a NSR investigation.

Under some circumstances, the IRB must determine whether a device involves significant risk (SR) or non-significant risk (NSR) to participants. Because NSR studies do not require an IDE, a clinical investigation involving an investigational device classified by the sponsor as NSR may be submitted to the IRB for review without an IDE. The sponsor should provide the IRB with a risk assessment and the rationale used in making its NSR risk determination. In this situation, the IRB reviews the information and makes its own independent determination that the device is SR or NSR. The IRB rationale for making the NSR/SR determination must be documented in IRB minutes.

(1) If the IRB determines that the study involves a SR device (disagrees with the assessment of the sponsor), then it would be governed by the IDE regulations at 21 CFR 812. The IRB would notify both the investigator and the sponsor of its determination, and the sponsor would need to submit an IDE application to the FDA. The study could not begin until the FDA approves the IDE and the IRB approves the study.

(2) If the IRB determines that the device is classified as NSR (concurs with the assessment of the sponsor), the clinical investigation may begin once IRB approval is obtained since the submission of an IDE application to the FDA is not required. *(Note: The terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.)*

(3) If FDA agrees that a new device is substantially equivalent to a device already on the market, it can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE regulations, IRB review, and informed consent.

Adverse Events and Reporting Requirements. Some requirements for reporting AEs are the same; regardless of what sort of test article is used (e.g. a drug or a device).

(1) **General Investigator Responsibilities for Reporting Adverse Events (AEs):** FDA, VA, and DHHS regulations require **prompt** reporting to the IRB, FDA, OHRP, and the Office of Research Oversight (ORO) of any unanticipated problems involving risks to human participants and others.

(a) FDA interprets "any unanticipated problems involving risks to human participants" to mean "…an unexpected adverse experience that is not listed in the labeling for the test article. …including an event listed in the labeling …that differs …because of greater specificity or severity" (FR 28027).

(b) FDA interprets "…and others" to mean, "…persons who are participating in clinical trials under the same or similar protocols or who may be affected by products or procedures developed in those trials" (FR 28027).

The Principal investigator is responsible for promptly reporting serious and unanticipated AEs to the IRB.

(2) **IRB Reports to the R&D Committee**: The IRB provides notification of AEs to the R&D Committee in the IRB minutes.

Any AE information submitted to the sponsor by investigators should also be submitted to the IRB when summarizing their experience in the request for continuing review. In addition to providing prompt written notification to relevant Federal agencies, including ORO, FDA, and OHRP, of any unanticipated problems involving risks to participants or others, the IRB should also report the resolution of those problems.

AEs and Reporting Requirements – IDEs. FDA IDE (device) reporting requirements are similar but not exactly the same as for drugs and biologics.

(1) **Investigator to Sponsor**: FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect within 10 days of discovery.

(2) **Sponsor to FDA, Investigator, and IRB.** The sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to all reviewing IRB(s) within 10 working days of the sponsor's receipt of the information.

Expanded Access to Investigational Devices. According to the statute and FDA regulations, an unapproved medical device may normally only be used in human participants when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized by FDA to make unapproved devices available to patients/physicians faced with circumstances such as those described above. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Federal Food, Drug, and Cosmetic Act). The sponsor must be contacted, as the sponsor must submit a supplement to the IDE as part of the process. The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.

(1) **Single Patient/Small Group Access to Investigational Devices.** Allows access to a device where patient is not eligible for an ongoing clinical trial. The participant must have a serious condition/disease, with no alternative intervention available. Under some conditions, FDA may grant permission even if there is no pre-existing IDE.

(a) Participant must have a serious condition/disease, with no alternative intervention available.

(b) Must contact sponsor, asking to use device.

(c) Sponsor submits IDE supplement to FDA requesting waiver, providing justification for use (may be able to do, even if no pre-existing IDE).

(d) FDA issues response in 30 days or less (FDA must approve use).

(2) **Treatment Use/IDE (21 CFR 812.36).** Allows wider access to a device during the clinical trial or prior to final action on marketing application. Again, the participant must have a serious condition/disease, with no alternative intervention available.

(a) Participant must have a serious condition/disease, with no alternative intervention available.

(b) Must contact sponsor, asking to use device.

(c) Sponsor submits treatment IDE supplement (pre-existing IDE required).

(d) FDA must approve.

(3) **Continued Access to Investigational Devices.** Allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims. There must be a public health need for the device, as well as preliminary evidence that the device is effective.

(a) Public health need for the device.

(b) Preliminary evidence that the device is effective.

(c) No significant safety concerns identified for the proposed indication.

(d) Conducted under a formal protocol with controlled rate of enrollment.

(e) Can collect additional evidence of safety and effectiveness.

(f) May be used to address new questions regarding the investigational device, such as labeling claims.

(g) Sponsor submits IDE supplement.

(4) **Access under a formal protocol.** Access in a controlled rate of enrollment and with no significant safety concerns identified for the proposed indication.

IRB Findings and Determinations Where Documentation is Required by Regulation. While the regulatory agencies agree on what will be documented, the methods of documentation are not regulated. FDA guidance allows certain findings to be documented in other formats, such as reviewer checklists that are filed in the protocol files. Documentation shall be provided for the following items when appropriate:

(1) The level of risk of the research.

(2) The approval period for the research, including identification of research that warrants review more often than (at least) annually. Approvals are valid for a maximum of 365 days unless the IRB feels that potential risks are such that the review period should be for a shorter period.

(3) Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research (e.g., Cooperative Studies, or other collaborative research).

(4) Justification for waiver or alteration of informed consent, addressing each of the four (4) criteria at 38 CFR 16.116(d). *(Note: This cannot be done if a FDA test article is involved.)*

(5) Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at 38 CFR 16.117(c).

(6) The special protection warranted in specific research projects on groups of participants who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research. For proposals that identify the potential for enrolling participants who could be vulnerable to coercion or undue influence, the IRB documents its consideration of additional safeguards to protect the rights and welfare of vulnerable participants.

(7) Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special 45 CFR 46.101(i) DHHS waiver or the FDA exception at 21 CFR 50.24.

(8) Consideration of the impact of study design on risk.

(9) Consideration of provisions for safety monitoring.

(10) Determination that risks has been minimized to the extent possible.

(11) Determination of the risk level of investigational devices.

(12) The interval of continuing review is at least once per year.

(13) The interval of continuing review is appropriate to the degree of risk.

(14) Approval of research on the basis that risks to participants are reasonable in relation to anticipated benefits (if any) to participants, and the importance of the knowledge that may be expected to result from research.

TITLE	**Emergency Use of an Investigational Drug or Biologic**	
Document number	**IRB-017**	
Effective Date	**January 27, 2005**	**Supercedes Document Dated: 09/07/2004**

1 POLICY

It is Stratton VA Medical Center's policy to comply with all applicable federal, state, and local regulations, and ICH guidelines in the use of investigational drugs and biologics.

2 DEFINITIONS – Refer to Appendix A

3 FORMS

N/A

4 REFERENCES

45 CFR 56.116(f)

21 CRR 50.23(a) and .23(c)

21 CFR 56.102(d) and .104(c)

FDA Information Sheets:
www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#emergency

5 PROCEDURE

5.1 An attending physician who desires to use an investigational article on an emergency basis must obtain clearance. During normal business hours the Research Office should be contacted to arrange clearance from the IRB Chair or designee, or the hospital administrator on-call.

5.1.1 After business hours, when there is not enough time to wait until the next business day, the IRB Chair or designee, or hospital administrator on-call should be contacted directly.

5.2 If time permits for a convened meeting of the IRB with a quorum, the IRB will consider approval of use.

5.3 If there is insufficient time to convene and IRB meeting, to provide clearance of the use of an investigational article without prior IRB approval, the IRB Chair or designee, or the hospital administrator on call must confirm that:

5.3.1 The attending physician affirms and will certify in the medical record that the subject is confronted by a life-threatening or severely debilitating situation necessitating the use of the investigational article, no standard acceptable treatment is available, and there is not sufficient time to obtain IRB approval.

5.3.2 The attending physician will obtain written informed consent from the subject (if the subject is 18 years old or older and is mentally capable of giving consent), from the subject's legally authorized representative (if the subject is not mentally capable of giving consent), or document in the medical record the situation is exempt from consent as follows:

5.3.2.1 If time is sufficient to obtain the determination of an independent physician who is not participating in the clinical investigation, the independent physician will certify in the medical record that:

5.3.2.1.1 The subject is confronted by a life-threatening situation necessitating use of the test article.

5.3.2.1.2 Informed consent cannot be obtained because of an inability to communicate with, or legally obtain, effective consent from the subject.

5.3.2.1.3 Time is not sufficient to obtain consent from the subject's legally authorized representative.

5.3.2.1.4 No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

5.3.2.2 If time is not sufficient to obtain the determination of an independent physician who is not participating in the clinical investigation:

5.3.2.2.1 The attending physician will certify items 5.3.2.1.1 thorough 5.3.2.1.4 are in the medical record.

5.3.2.2.2 The attending physician will certify in the medical record that informed consent cannot be obtained because of an inability

to communicate with, or legally obtain consent from the subject's legally authorized representative.

5.3.2.2.3 The attending physician will certify in the medical record that time is not sufficient to obtain the determination of an independent physician who is not participating in the clinical investigation.

5.3.2.2.4 Within 5 business days after use of the article, the attending physician will have the determination reviewed and evaluated by an independent physician.

5.3.2.2.5 The attending physician should notify the subject directly of the emergency use once/or if the subject's condition permits.

5.3.2.2.6 The attending physician should notify the subject's legally authorized representative as soon as possible and obtain written consent to continue any procedures related to the investigational article.

5.3.3 The attending physician will forward a letter to the IRB Chair confirming the emergency use of the investigational article within 5 business days. The letter must be dated, identify the subject's initials including the subject's last 4 numbers of their social security number, briefly describe the subject's medical condition necessitating the use of the investigational article, and confirm the absence of a standard acceptable treatment. A copy of the consent document, if obtained, must be attached to the letter.

5.3.4 The IRB Chair will forward a letter to the attending physician acknowledging the receipt of the letter describing the emergency use of the investigational article and will request the attending physician present a new protocol submission to the IRB or a letter of explanation.

5.3.5 The attending physician, if applicable, will submit a protocol in time for the next deadline of the monthly IRB meeting.

5.4 The IRB Chair or designee, or hospital administrator on-call providing clearance after business hours will notify the Research Office of the emergency use verbally by, or on the next business day.

5.5 Attending physicians who fail to submit a letter to the IRB Chair confirming the emergency use of the investigational article within 5 business days or a new protocol submission to the IRB following emergency use of an investigational article become ineligible to submit new protocols to the Stratton VAMC IRB, and maybe reported to oversight agencies, if appropriate.

5.5.1 Attending physicians remain ineligible until a new protocol submission or letter of explanation is received and approved by the IRB.

5.5.2 Currently approved research is not affected by an attending physician's ineligible status.

5.5.3 The list of ineligible attending physicians will be distributed to IRB members with the agenda and included with the meeting minutes.

5.5.4 Attending physicians will be notified of their ineligible status in the Notification of Ineligibility.

5.5.5 The IRB Chair or designee may remove attending physicians from the ineligible list when the attending physician cannot comply with the requirements to submit a new protocol due to circumstances beyond his or her control. Such circumstances may include, but are not limited to, interim approval of the drug, device, or biologic by the FDA or non-cooperation by the sponsor. In this case, the IRB Chair or designee will accept a letter from the attending physician stating the circumstances.

5.6 The need for an investigational drug that does not as yet have an IND may arise in an emergency situation that does not allow time for submission of an Investigational New Drug (IND) application. In such a case, the FDA may authorize shipment of the test article in advance of the IND submission. Attending Physicians may request such authorization by contacting the FDA using the FDA Emergency Use Phone Number List.

5.7 Emergency Use of an investigational drug or biologic by an attending physician will be included as a business item in the next scheduled IRB meeting agenda.

Information Sheet

Emergency Use of Investigational Drug or Biologic at the Stratton VAMC:

1. Obtaining an Emergency IND

The emergency use of an unapproved investigational drug or biologic requires an IND. If the intended subject does not meet the criteria of an existing study protocol, or if an approved study protocol does not exist, the usual procedure is to contact the manufacturer and determine if the drug or biologic can be made available for the emergency use under the company's IND.

The need for an investigational drug or biologic may arise in an emergency situation that does not allow time for submission of an IND. In such a case, FDA may authorize shipment of the test article in advance of the IND submission. Requests for such authorization may be made by telephone or other rapid communication means. (21 CFR 312.36).

Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.102(d)] is an exemption from prior review and approval by the IRB. The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval. FDA acknowledges, however, that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue.

2. Institutional Procedures may require that the IRB be notified prior to such use; however, this notification should not be construed as an IRB approval. Notification should be used by the IRB to initiate tracking to ensure that the investigator files a report within the five day time-frame required by 21 CFR 56.104(c).

3. An IRB must either convene and give "full board" approval of the emergency use or if the full conditions of 21 CFR 56.102(d) are met and it is not possible to convene a quorum within the time available, the use may proceed without IRB approval.

4. Exception from Informed Consent Requirement

Even for an emergency use, the investigator is required to obtain informed consent of the subject or the subject's legally authorized representative unless both the investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following [21 CFR 50.23(a)]:

a. The subject is confronted by a life-threatening situation necessitating the use of the test article.

b. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject's legal representative.

c. Time is not sufficient to obtain consent from the subject's legal representative.

d. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

5. The investigator must notify the IRB within 5 working days after the use of the test article [21 CFR 50.23 (c)}.

APPENDIX A

DEFINITIONS:

Adverse event: Any unfavorable or unintended physical, legal, social, economic or psychological harms or injury, improper disclosure of private information, or any unanticipated problem that occurs associated with a research study, including abnormal lab findings, symptoms, or disease. An adverse drug experience or adverse device event is considered to be an adverse event. An AE may occur even in the absence of any error or protocol deviation, and does not necessarily have to be caused by any identifiable aspect of the research.

Advertising: Media intended to recruit prospective subjects to participate in research. This does not include media (1) authored by someone other than the sponsor and VA employees or agents; (2) intended to be read solely by VA employees who are not intended to be subjects and limited to study name, inclusion and exclusion criteria and contact information; or (3) documents intended for internal use by the study's research staff. Media includes, but is not limited to newspaper, radio, TV, bulletin boards, posters, brochures, flyers, and web pages.

Approval Date: The date of the initial or most recent continuing approval of research by the IRB as documented on correspondence to the Principal Investigator.

Assent: An affirmative agreement to participate in research. Failure to object should not be construed as assent.

Attending Physician: Physician directly responsible for care of the subject.

Case History: A case history is a record of all observations and other data pertinent to the investigation on each research subject. An investigator is required to prepare and maintain adequate and accurate case histories. Case histories include the case report forms and supporting data including signed and dated consent forms, any medical records including , but are not limited to: progress notes of the physician, the individual's hospital chart(s), and nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

Closure: All research related activity has been completed or was never started.

Co-investigator: Individual(s) who has substantial involvement and directly aides the Principal Investigator(s) in the conduct and oversight of the study.

Conflict of Interest (COI): A conflict of interest occurs when any financial arrangement, situation or action affects or is perceived to exert inappropriate influence on the design, review, conduct, results or reporting of research activities or findings. The impact of the conflict may occur in any phase of the research from the development of the study design, to the consenting of research subjects, and to the management of the study. The conflict may also bias review of proposals, analysis of data and dissemination of research results through publications and presentations.

Deviation: Any departure from the procedures stated in the approved research protocol or informed consent without prior review and approval of the modification.

"Significant Deviations": Any departure from the procedures stated in the approved research protocol or informed consent that increases the risk to subjects and is required to be reported to the IRB within 5 days of the incident. Examples include but are not limited to the following:

- Infractions involving dosing/distribution of study medications causing risk to the subject
- Infractions in following the guidelines for proper informed consent execution (i.e. using an expired informed consent)
- Infractions in which the sponsor (if applicable) requests notification to the IRB
- Infractions in which procedures were performed outside the approved research protocol

"Non-Significant Deviations": Any departure from the procedures stated in the approved research protocol or informed consent that pose no increased risk to the subjects and do not require reporting to the IRB. Examples include but are not limited to the following:

- Infractions involving expected concomitant medication deviations
- Infractions involving missed/late visits that pose no increased risk to the subject
- Infractions involving unintentional clerical errors on the informed consent (i.e. subject identifiers are not on all pages)

DSMB (Data Safety Monitoring Board): Responsible for safety monitoring in a multicenter clinical trial. The board should provide an IRB with safety information in a digestable format, at appropriate intervals that will allow the IRB, together with investigators, to perform a more reliable assessment of the significance of AE data in terms of protection of human subjects.

Emergency Use: The use of an investigational drug or biological product with a human subject in a life-threatening or severely debilitating situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval. Emergency use of an investigational drug or biologic is not considered research according to 45 CFR 46.116(f).

Emergency Use Research: Use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

Expected Adverse Event: For approved and marketed drugs or devices, those adverse events described in the approved package insert, and for investigational new drugs or devices, those adverse events described in the FDA Investigator's Brochure.

FDA Regulated Test Article: Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act.

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Health Information: Health information is any information created or received by a health care provider or health plan that relates to: the past, present, or future physical or mental health or condition of an individual; the provision of health care to an individual; or payment for the provision of health care to an individual. This encompasses information pertaining to examination, medical history, diagnosis, findings or treatment, including such information as: laboratory examinations, X-rays, microscopic slides, photographs, prescriptions, etc.

Human Subject: A living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information, or individual who is or becomes a subject in research, either as a recipient of an FDA regulated test article or as a control. A subject may be a healthy individual or a patient.

Identifiable Private Information: Private information in which the identity of the subject is or may readily be ascertained by the investigator, or the identity of the subject is associated with the information.

Imminent Threat of an AE in Research: Any situation in which an AE in research has not yet occurred but is likely to occur, as determined by an IRB, research, or clinical team member, without preventative measures.

Impartial Witness: A person, independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally authorized representative cannot read, and who reads the informed consent document and any other written information supplied to the subject.

Individually-identifiable Health Information: Individually-identifiable health information (IIHI) is a subset of health information, including demographic information collected from an individual, that is: (1) created or received by a health care provider, health plan, or health care clearinghouse; (2) related to the past, present, or future condition of an individual and provision of, or payment for health care; and (3) Identifies the individual or a reasonable basis exists to believe the information can be used to identify the individual.

Institutional Review Board (IRB): The Stratton VA Medical Center Institutional Review Board, formally designated by Stratton VA Medical Center to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human subjects.

Intervention: Physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Interventional studies: Studies that include research designed to evaluate the safety, effectiveness, or usefulness of therapies (i.e. drugs, diet, exercise, surgical interventions,

or medical devices), diagnostic procedures (i.e. CAT scans or prenatal diagnosis through amniocentesis, chorionic villi testing, and fetoscopy, or preventive measures (i.e. vaccines, diet, or fluoridated toothpaste).

Investigational Article: A drug or biologic classified by the Food and Drug Administration as investigational.

IRB Chair: The person responsible for the oversight of the review functions of the IRB.

IRB Chair designee: An IRB member with one or more years of experience on the IRB.

IRB Member: A voting member of the IRB or non-voting ex-officio members.

IRB Staff: Members of the Research Office who support the functions of the IRB.

Legally authorized representative: An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. Legally authorized representative is synonymous with legally acceptable representative.

Life-Threatening: Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted and diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival. The criteria for life-threatening do not require the condition to be immediately life-threatening or to immediately result in death. Rather, the subjects must be in a life-threatening situation requiring intervention before review at a convened meeting of the IRB is feasible.

Minimal risk: Risk in which the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Non-interventional studies: Studies on normal human functioning and development that involve limited invasive or non-invasive procedures i.e. blood or urine collection, moderate exercise, fasting, feeding, sleep, learning, responses to mild sensory stimulation, surveys or questionnaires, etc. are, for the purposes of this policy, considered non-interventional studies.

Observational studies: Studies include research that does NOT involve any intervention, alteration in standard clinical care or use in subjects of any invasive or non-invasive procedure. Studies limited to the recording of data on individuals receiving standard medical care, the use of existing specimens or data, or the retrospective review of health information are considered observational studies.

Off-site Event: Any adverse event experienced by a human subject enrolled in research at a site other than the Albany VAMC (i.e. multisite research).

On-site Event: Any adverse event experienced by a human subject enrolled in research at the Albany VAMC (regardless of where the

event occurs).

Participant: Personnel who participate in the mandatory training for investigators.

Primary Reviewer: Any member of the IRB, based on their area of expertise, who is assigned by the IRB staff with the concurrence of the IRB Chair or designee, and is not participating in the research.

Principal Investigator(s): Individual(s) who actually conducts a research investigation under whose immediate direction research is conducted, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of the team.

Private information: Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Progress Report: The completed progress report form and submitted attachments.

Progress Report Deadline: Approximately three weeks before the date of the IRB meeting at which continuing review is scheduled to occur. The progress report deadline may be extended to accommodate those reports received after the deadline if there is adequate time for review by the IRB staff and members.

Quorum: Minimum number of voting members who must be present at the meeting for business to be legally transacted, and includes at least one member whose primary concern is in a non-scientific area.

Research: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge or any experiment that involves an FDA regulated test article.

Research Compliance: The person or organizational element, except the Principal Investigator, designated by management to perform the duties relating to quality assurance and compliance of clinical research studies.

Research & Development Committee (R&D): Reviews the scientific quality and appropriateness of research and development projects, human rights, laboratory safety, and welfare of animals in research, regardless of funding source. Human subject research may not begin without final R&D approval.

Serious Adverse Event: Any adverse experience that results in any of the following outcomes or requires medical or surgical intervention to prevent any of the following outcomes: Cancer, congenital anomaly/birth defect, death, hospitalization, life-threatening experience, persistent or significant disability/incapacity, prolongation of existing hospitalization, or overdose.

Severely Debilitating: Diseases or conditions that cause major irreversible morbidity. Examples of severely debilitating conditions include blindness, loss of arm, leg, hand or foot, loss of hearing, paralysis, or stroke.

Standard Operating Procedure (SOP): A procedure written in standardized format, giving detailed instructions, which describe a routine activity so that each person following the SOP will perform the activity in a consistent and repeatable manner. The SOP author is responsible for technical content of the SOP.

Sub-investigator: All others involved in the study such as research coordinator(s), research pharmacist(s), other clinical providers who are authorized to prescribe study-related medications, and other ancillary personnel.

Suspension of research: A directive of the IRB or the IRB Chair or designee to temporarily or permanently stop some or all recruitment, or some or all of the research activities.

Termination of research: A directive of the IRB to withdraw approval for research.

Unanticipated Adverse Device Effect: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Unexpected Adverse Event: Any adverse event, the specificity or severity of which is not consistent with the risk information previously reviewed and approved by the IRB. All unanticipated adverse device events are considered to be unexpected adverse events. If the nature and severity of an adverse event are accurately reflected in the consent document, then the IRB considers the adverse event to be expected.

Unexpected Problem: Synonymous with unexpected adverse event.

Unexpected Problem Involving Risks to Subjects or Others: An unexpected problem that indicates a substantial change in the risk benefit profile of a research protocol.

Vulnerable Subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

APPENDIX B

REFERENCES:

Categories of Research That May be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure (*Federal Register*, Vol. 63, No. 216, Monday November 9, 1998)

Department of Health and Human Services (DHHS) regulations pertaining to rights and welfare of human subjects participating in research supported by DHHS (45 CFR 46)

FDA Information Sheets 1998 Update
www.fda.gov/oc/ohrt/irbs/drugsbiologics.html#emergency

Food and Drug Administration (FDA) regulations pertaining to rights and welfare of human subjects participating in research involving investigational drugs and devices (21 CFR 11, 50, 56, 312, 812, and 814)

ICH Harmonised Tripartite Guideline For Good Clinical Practice (1 May 1996)

M-3, Part 1, Chapter 3 Functions of the Research & Development Committee

M-3, Part 1, Chapter 15 Misconduct in Scientific Research

NYS Public Health Law

Pharmacy Memorandum D&T 119-9

Robert's Rules of Order, 10th Edition

Station Memorandum SL-151-04: Institutional Review Board

Statutes and regulations pertaining to the release of patient information (5 USC &522a; 38 USC & 5701a, 7332; 45 CFR Parts 160-164)

Statutory Provision for the Protection of VA patient rights (38 USC Sections 501, 7331)

Stratton VA Medical Center R&D SOP

VA regulations pertaining to hospital care for research purposes and outpatient care for research purposes (38 CFR 17.45, 17.92)

VA regulations pertaining to research related injuries (38 CFR 17.85)

VA regulations pertaining to the rights and welfare of human subjects participating in research (38 CFR 16 – Federal Policy for the Protection of Human Subjects- The Common Rule)

VHA Directive 2000-043 Banking of Human Research Subject's Specimens

VHA Handbook 1058.1 Reporting Adverse Events in Research to the Office of Research Oversight

VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research

VHA Handbook 1200.13 Conflict of Interest in Research

VHA Pharmacy Manual, M-2, Part VII, Chapter 6 and Chapter 5.10

APPENDIX C

Standard Operating Procedure

Research Related Complaints and Allegations of Non-Compliance

1. This standard operating procedure will:
   i) describe the processes available for receiving, responding to, and reporting research related complaints and allegations of non-compliance with medical center policies and procedures as well as regulatory requirements and ethical treatment of subjects.
   ii) include a process for the required investigation and established remedial action for and consequences of findings of noncompliance with HRPP and IRB policies.
   iii) describe the process for reporting to institutional officials and other appropriate parties and authorities.

2. There are numerous avenues for reporting available at the Stratton VA Medical Center. These mechanisms provide for responding, reporting and tracking of research related complaints or allegations of noncompliance. Stratton VA Medical Center policies make provision for investigation and remedial action. Complaints may be verbal or written. They may include reports of investigator noncompliance with IRB-approved protocol s, repeated and continuous failure of the investigator to report required or requested information to the IRB, and reports of research publications authored by investigators for which there is no approved protocol. Reports may also include audits, both internal and external, with findings of noncompliance with regulatory or ethical principals of human research.

3. Research related complaints and allegations of non-compliance can be reported to any of the following, as appropriate:

- area supervisor or designated point of service contact;
- ACOS, Research ;
- Research Compliance Officer;
- Medical Center Compliance Officer;
- Risk Manager;
- Patient Safety Officer;
- Patient Advocate;
- Institutional Review Board;
- Ethics Advisory Committee;
- Telecare (1-888-838-7898);
- 24 hour 1-800-223-4810 Help-line
- VA website QUIKCARD;
- VHA National 24 hour compliance helpline 1-866-842-4357.

4. The general route for patient, subject and family complaints and concerns is via the Patient Advocate. The Network 2 Medical Outcomes Disclosure Program 10N2-153-01, the Network 2 Veteran Customer Service Program Memorandum, 10N2-184-04, the Patient Advocate Program and Tracking Package, the Ethics

Advisory Committee Memorandum MVAC 00-72, and the Network 2 Compliance and Business Integrity Program Memorandum 10N2-174-03 all describe the mechanism for receiving and responding to veterans, families, staff and other sources. These policies aim to identify the source(s) of a given complaint or allegation and describes the delegation and referral process involved in resolving, responding and referring issues that can not be resolved directly. The research informed consent form provides the subject with the telephone number of the Patient Advocates at each respective site, in addition to the Research Office (ACOS, IRB Chair) for questions that the subject may have regarding their rights. The Patient Advocate Program identifies the ACOS/R&D and the Research Compliance Officer as the Point-of-Service contacts for patient complaints and complaints of noncompliance. The ACOS/R&D and the Research Compliance Officer will report to the Chair of the IRB, the Chair of R&D and to institutional officials all complaints or allegations of non-compliance. The Patient Advocate and the Risk Manager will also receive a report.

5. The specific process for receiving, handling and responding to research-related complaints and allegations of non-compliance are contained in several policies referenced in the following discussion.

6. Initial Investigation and Action: The ACOS/R&D, the Chair of the IRB, the Chair of R&D or the Research Compliance Officer will obtain as much information as possible from the individual reporting the event. If the incident can not be resolved immediately, a meeting will be arranged by the ACOS/R&D. The attendees will be determined by the ACOS/R&D and is dependent on the circumstances and severity of the complaint or allegation of non-compliance. The process will include:

INR 1C (4)

- Description of the incident and the facts presented to date.
- List of attendees required for the meeting, to be held within 72 hours of the report, whenever feasible.
- Discussion and decision as to whether the protocol should be put on administrative suspension, such that no additional subjects are enrolled or all activities are temporarily suspended. Initial decisions will be based on preliminary information and the seriousness of the complaint.
- If a suspension of the protocol is not merited, the IRB, IRB Chair or designee, the ACOS/R&D and the responsible investigator(s) will resolve the complaint or forward to the IRB for action.
- The responsible investigator(s) and appropriate department heads and agencies are notified of the decision by the ACOS/R&D. Correspondence will be sent to the complainant by the ACOS/R&D acknowledging receipt of the complaint or allegation of non-compliance and indicating that the issue is being investigated.

The Institutional Official is notified immediately after these initial decisions are made. Administrators will determine whether an administrative investigation is required in cases of possible “Misconduct in Scientific Research”. The Network 2 Medical Staff/Professional Peer Review Policy 10N2-52-03 establishes the process for systematic, fair, and comprehensive review in cases that involve clinician variations from accepted standards of practice. M-3 Part 1, Chapter 15 entitled “Misconduct in Scientific Research” describes the process for submitting and addressing complaints or allegations related to fabrication, falsification, or

plagiarism. The policy addresses the process for fact finding and investigation as well as defining consequences and corrective actions. This policy assures anonymous reporting.

IRB Committee Review Process: The convened IRB is notified of the incidents and action taken at the next scheduled meeting by the ACOS/R&D. The IRB will determine if outstanding issues exist and what actions should be taken. The IRB will determine if any action should be taken such as protocol suspension, placing hold on accrual, or no action. Such action must take into consideration any potential effects on current research subjects' safety and well-being. Any suspensions or Closures of approval shall include a statement of reasons for IRB's action. A vote to continue to suspend or terminate approval will be reported immediately to the investigator(s), Institutional Officials, ORO, OHRP, the FDA if the research is regulated by the FDA and to sponsor(s) and other applicable agencies. All communications will be documented in the IRB minutes.

IRB 3B (5)

IRB Actions of Outstanding Issues: If an issue of non-compliance with research policy is raised, the IRB or designee such as the Research Compliance Officer will conduct a review of the investigator records and may also observe the consent process of an ongoing study. Continuous monitoring of ongoing studies will be conducted by a member of the IRB or designee, such as the Research Compliance Officer to ensure corrective action has occurred and the research is conducted in accordance with all regulations and policies as required by the institution. These reviews may include:

(1) Determining whether the investigator has complete copies of all signed informed consents in his/her files for each research study on which they are the principal investigator.

(2) Conducting chart reviews to determine if copies of the informed consent documents are in the subject's medical record.

(3) Determining whether the investigator has a copy of the current protocol and an unsigned copy of the most recent informed consent document for their study and it contains a stamp with the correct expiration date.

(4) Determining whether the investigator has complete and current copies of all correspondence on the study from the Research Office and, if applicable, the study sponsor.

IRB 3C (2)

CRB 3A (1)

CRB 2A (1)

(5) The IRB will review any reports of serious adverse events, communication from the sponsor regarding subject safety, if applicable, and determine whether the risk has changed and whether the consent needs to be revised. If there is an indication of a change in risk vs. benefit based on the literature review or reports of serious adverse events, the IRB will determine whether the informed consent form with HIPAA provisions or separate HIPAA authorization requires changes, whether the study may continue, may continue with modification, needs to be monitored more frequently, or if the study should be suspended or terminated.

(6) In the event that there are allegations of a significant departure from accepted practices of the relevant scientific community, the IRB may require the investigator to provide the IRB with relevant original or photocopied records of the study in question.

(7) In the event that the incident appears to be isolated, of a non-serious and non-continuing nature, the incident will be handled internally. The investigator will receive written communication describing the incident and summary of the audit from the Research Compliance Officer. A response from the investigator describing corrective actions will be required within 5 days of the date of the letter, The IRB or IRB Chair or designee will determine if corrective action is appropriate.

Reporting Process: The results of investigations will be reviewed and approved by the IRB and R&D Committees and if necessary, reported to other appropriate entities and authorities as required. Outcomes and notification of progress of complaints will be communicated to the individual by the Chair of the IRB, ACOS/R&D, institutional official or Office of Research Oversight, as defined in Memorandum: What to report to ORO dated November 12, 2003. The Research Compliance Officer will track all complaints and allegations of noncompliance to ensure timely resolution and reporting.

INR 1C (1), (2), (3), (4)

IRB Committee Monitoring Process: The monitoring process will include review of any complaints, allegations or findings of non-compliance with institutional policies, and/or of scientific misconduct reported to the IRB. Research subjects and research personnel are instructed to report such incidents to the Research Office, Chair of IRB, Chairperson of the R&D Committee or Research Compliance Officer. Research subject surveys about the participants experience during the informed consent process, research staff interviews, surveys and other methods are used to provide feedback about the research program at the Stratton VA Medical Center.
The ACOS/R&D will report to the IRB as part of the performance improvement program. The Chairs of the IRB and R&D Committee in consultation with the ACOS/R&D will ensure a response to each question, concern, or complaint, and the investigation of complaints and allegations. Depending on the concern or issue, the Chair of the R&D Committee, Chair of the IRB and/or ACOS/R&D will assist in the monitoring of remedial action for findings of non-compliance with HRPP and IRB policies. Minutes of IRB and R&D Committees will report review and outcome of complaints.

7. Information from staff related to adverse events involving research subjects are reportable as described in the IRB SOP 008 Processing of Adverse Event, Injury or Unanticipated Problem, the Network 2 Integrated Safety/Risk Management Program 10N2-29-03. These describe the reporting, investigation, analysis and corrective action process for adverse events. Investigators must notify the IRB of any serious adverse event or unanticipated problem as soon as possible and no later than 5 business days after identification of the event.

8. M-3 Part 1, Chapter 15 entitled “Misconduct in Scientific Research” describes the process for submitting and addressing complaints or allegations related to

fabrication, falsification, or plagiarism . The policy addresses the process for fact finding and investigation as well as defining consequences and corrective actions. This policy assures anonymous reporting.

9. The Ethics Advisory Committee Memorandum MVAC 00-72 is available for support and consultation for any veteran or staff member who has an ethics related concern. The policy describes the process of requesting a consult, the review process, documentation and recommendation procedures. Patients and family members are provided with brochures in their Patient Information envelope. This information is also found in the Patient and Visitor Handbook located in the ER, Clinics and Hospital Rooms.

10. The Network 2 Medical Staff/Professional Peer Review Policy 10N2-52-03 establishes the process for the systematic, fair, and comprehensive review in cases that involve clinician variations from accepted standards of practice.

This document describes local reporting of research complaints and allegations of non-compliance with medical center policies and procedures as well as regulatory requirements and ethical treatment of subjects. Additional external avenues are available for reporting: VA Office of the Inspector General (OIG), VA Office of Research Oversight (ORO); Department of Health and Human Services Office of Human Research Protection (OHRP); Department of Health and Human Services Food and Drug Administration (FDA).

References:

Network 2 Veteran Customer Service Program Memorandum, 10N2-184-04
Network 2 Patient Advocate Program 10N2-86-03
The Patient Advocate Program and Tracking Package
Ethics Advisory Committee Memorandum MVAC 00-72
Network 2 Medical Outcome Disclosure Program 10N2-153-01
Network 2 Integrated Safety/Risk Management Program 10N2-29-03
Network 2 Medical Staff/Professional Peer Review Policy 10N2-52-03
Network 2 Medical Staff/Professional Peer review Policy 10N2-52-03
Compliance Inquiry Policy VHA Directive 2001-051
VHA Network Upstate New York Compliance and Business Integrity Program Memorandum 10N2-174-03
Network 2 Patient Envelope N102-184-04